NEUROPSYCHOLOGICAL CHARACTERISTICS OF POSITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: IMPLICATIONS FOR COGNITIVE REMEDIATION

By

© DANIEL RALPH BIRD, B.A., M.A.Sc.

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Doctor of Philosophy

McMaster University

January, 1990

NEUROPSYCHOLOGICAL CHARACTERISTICS OF POSITIVE VERSUS NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

DOCTOR OF PHILOSOPHY (1990)
(Medical Sciences)

McMaster University
Hamilton, Ontario

TITLE: Neuropsychological Characteristics of Positive and Negative Symptoms in Schizophrenia: Implications for Cognitive Remediation

AUTHOR: Daniel Ralph Bird, B.A. University of Waterloo
M.A.Sc. University of Waterloo

SUPERVISOR: M. Alan J. Finlayson, Ph.D.
Professor, Department of Psychiatry

NUMBER OF PAGES: vii, 236

ABSTRACT

This study examines the relationship between neuropsychological functioning and positive versus negative symptoms of schizophrenia in order to test the hypothesis that negative symptoms are uniquely associated with cognitive deficits and attentional impairment. Forty chronic schizophrenics were subtyped on the basis of symptoms which were predominantly positive (n=10), predominantly negative (n=10), both positive and negative (n=10), or neither positive nor negative (n=10) and administered a battery of neuropsychological tests. The possibility that patterns of deficits among subtypes, if found, reflect lateralized or localized dysfunction was also examined.

Test data revealed that positive- and negative-symptom schizophrenics are equally impaired according to several global indices of neuropsychological functioning as well as on various measures of attention. These findings are inconsistant with the hypothesis that cognitive and attentional deficits are unique to negative-symptom schizophrenia as has been reported in the literature. Further analysis of deficit patterns revealed that positive-symptom schizophrenics, relative to the asymptomatic group, showed more marked deficits in verbal learning and memory whereas negative-symptom schizophrenics, based on identical comparisons, showed greater impairment on measures of fluency and productivity. No relation was observed between neuropsychological indicies of right versus left or, anterior versus posterior dysfunction and a patient's symptom status. In fact, low correlation between psychiatric symptoms and neuropsychological performance was generally observed. Reconceptualization regarding defining characteristics of positive- and negative-symptom syndromes, particularly with respect to assumptions about attention and cognition, is suggested.

The heterogeneity of neuropsychological deficits found among schizophrenics and their dissociation from the patients psychiatric presentation, stress the need for independent, individual assessment of cognitive functioning. Given that neuropsychological deficits, when identified, likely contribute to impaired social and occupational functioning, improvement in neuropsychological status may translate into improvement in these areas of everyday living. Preliminary results of an attempt at computer-based cognitive remediation in a selected subset of schizophrenics are presented and a neuropsychological approach to psychiatric rehabilitation is proposed.

ACKNOWLEDGEMENTS

I would like to thank, foremost, the members of my doctoral committee for their guidance, not only with respect to this dissertation project, but for the general nurturance and support they have shown both personally and professionally:

Jack Byles, D.S.W.
John M. Cleghorn, M.D.
M. Alan J. Finlayson, Ph.D., Chairman
Mani Van der Spuy, D.Phil.
Meir Steiner, M.D., Ph.D.

I further express my gratitude to the following clinicians who referred patients to my study. Without their co-operation the recruitment of subjects would have been an arduous task:

Tessie Abugan, R.N.
Mary Blenkharn, Grad. N.
Pat Brodie, R.N.
Coleen Clairmount, M.S.W.
Ferdi Coletto, R.N.
Winnie Doyle, R.N.
Pat Foley, M.D.
Bonnie Gillespie, M.S.W.
David Jewell, M.S.W.
Nick Kates, M.D.
Paul Links, M.D.
Neil McMahon, M.S.W.
Gloria Muller, R.N.
Jan Nicholson-Smith, M.S.W.
Trienke Niemeyer, M.S.W.
Sharon Orovan, R.N.
Kim Round, R.N.
Anita Spenser, M.S.W.
Sharon Woods, R.N.

I would like to also acknowledge the varied contributions of the following individuals who have supported this project with their skills and expertise: Dr. John Davis, Dr. Susan Denburg, Dr. Ron Kaplan, Ms. Nancy McEachen, Dr. John Schneider, Dr. Dave Streiner, and Dr. Jean Wallace.

Finally, I thank my friends and family for their support, encouragement and faith in my ability: Ralph and Vivian Bird, Reg and Barb Marratto, Sherrylynn Bird, Mary Ellen and Mario Turco, Paul and Rebecca Bazely, Wendy & Jerry Mariani and Gary, Brad and Paul Marratto.

IN MEMORIUM

JACK BYLES, D.S.W.
1923 - 1987

I would like to acknowledge the contribution of Dr. Jack Byles who served as a member of my supervisory committee from 1982 until his death due to cancer in 1987. Dr. Byles remained actively involved with this project throughout the course of his illness and will be remembered not only for relentless dedication to his work but for his warm and humble demeanor.

DEDICATION

This thesis is dedicated to my daughter, Sarah Ashley Bird.

TABLE OF CONTENTS

NEUROPSYCHOLOGICAL CHARACTERISTICS OF POSITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: Implications for Cognitive Remediation

Overview

The idea that schizophrenic symptoms are related to underlying brain pathology has received substantial support in recent years. Research using sophisticated brain-imaging techniques shows that a significant portion of schizophrenics have gross structural brain abnormalities. Other evidence suggests that neurochemical changes are also present in the brains of many schizophrenics. These structural and biochemical changes appear unrelated to the effects of treatment or aging.

The identification of structural and biochemical abnormalities in schizophrenia is important because etiology of lesion implies a separate intervention and prognoses. Symptoms associated with biochemical abnormality can be controlled, or at least alleviated, through treatment with neuroleptic drugs (Johnstone, Crow, Frith, Carney & Price, 1978). On the other hand, symptoms associated with structural brain changes do not respond to neuroleptics, in fact, many are exacerbated by pharmacological intervention (Angrist, Rotrosen & Gershon, 1980). In addition, structural changes are frequently

associated with generalized cognitive impairment, which, combined with a poor response to neuroleptics, yields a poor prognosis (Crow, 1980).

It has recently been hypothesized that there are two syndromes of schizophrenia (Crow, 1980, Andreasen, 1982). According to Crow (1980) one syndrome (Type I) is characterized by positive symptoms (e.g., delusions, hallucinations, thought disorder), neuroleptic responsivity, biochemical abnormality and no cognitive impairment and the other (Type II) by negative symptoms (e.g., affective flattening, poverty of speech and social withdrawal), structural brain changes, neuroleptic nonresponsivity, and cognitive impairment.

Whereas the heuristic importance of the two-syndrome hypothesis is clear, the validity of these fundamental assumptions remain largely unchallenged. In particular, the assumption that negative symptoms are uniquely associated with cognitive deficits has received little attention from researchers. One focus of this study is, therefore, to investigate the neuropsychological characteristics of patients exhibiting positive versus negative symptoms of schizophrenia (Study I).

In addition to its theoretical significance, the identification of cognitive impairment among any subgroup of schizophrenics is important because programs to remediate or, at least, ameliorate those deficits are now

being developed; however, many of these programmes were developed for individuals who sustained traumatic brain injury. Given that the neuropsychological profiles of minor head injury patients and schizophrenics are often indistinguishable (Newlin, 1983) the usefulness of these programs to schizophrenic patients whose symptoms also appear to reflect brain dysfunction will be explored (Study II).

In the sections which follow, three bodies of literature are reviewed. Initially, the history of the nosology of schizophrenia is presented up to and including recent neurodiagnosic and neuropsychological data which suggest underlying brain dysfunction in a substantial proportion of schizophrenics. This literature is followed by an examination of studies which suggest dividing schizophrenic patients according to positive and negative symptoms may provide a valid subtyping schema with separate etiologic, prognostic and treatment implications. This literature is reviewed in the context of Study I which examines the neuropsychological characteristics of positive- versus negative-symptom schizophrenia. A third body of literature relates to cognitive remediation techniques and their potential suitability to schizophrenics whose poor prognosis appears related to underlying neuropsychological deficits and brain dysfunction. This literature is examined in the context of

Study II in which preliminary results of an attempt at computer-based cognitive remediation, in a small sample of schizophrenics, are presented.

It should be noted that Study I and Study II were run concurrently and that the cognitive remediation study (Study II) was not fashioned on the basis of results from Study I.

SCHIZOPHRENIA: HISTORICAL ASPECTS

Schizophrenic disorders were at one time attributed to a type of "mental deterioration". The term "dementia praecox" was first adopted by the German psychiatrist Emil Kraepelin, in 1896, to describe a mental illness characterized by early onset and chronic deterioration (Tsuang, 1982). Kraepelin's contribution was to describe and identify two specific types of major psychiatric illness. Based on clinical observation, he noted that some patients, who had a specific set of symptoms, often recovered spontaneously with minimal treatment, while other patients rarely recovered, usually deteriorated, and required lifetime institutionalization. He further noted that those patients who tended to recover also tended to have symptoms of either euphoria with increased energy or dysphoria with decreased energy. He placed these patients together in a single group because they had a similar clinical course and prognosis, despite their diverse

symptomatology, and called their illness "manic-depressive insanity". The second group of patients that he identified were persons who became ill at a relatively young age, suffered also from diverse symptoms (e.g., delusions, hallucinations, excitement, confusion, depression, elation), and tended to deterioriate slowly but progressively until they became completely incapacitated. He named their illness "dementia praecox" ("dementia" referring to the characteristic deterioration and "praecox" in view of the early age of onset)(Andreasen, 1984, pp. 15-16). In his writings Kraepelin stressed the difference between the progressive/deteriorating course of dementia praecox and the episodic recurrence of manic-depressive illness. Kraepelin´s identification of these two forms of major psychiatric disorder still stands as a significant contribution to our conceptualization of mental illness (Tsuang, 1983).

The term "schizophrenia" was first introduced by the Swiss psychiatrist Eugen Bleuler in 1911 (Hamilton, 1984) to describe the splitting of mental functions in those patients described as suffering from dementia praecox (derived from the Greek words "schizein" which means "to split" and "phren" which means "mind"). Bleuler continued the work of Kraepelin but argued that dementia praecox did not invariably lead to deterioration and that its onset was not confined to adolescence as Kraepelin had earlier

supposed (Coleman, 1976).

Although descriptions of schizophrenia often suggest a unitary disorder, schizophrenia actually consists of various subtypes (Tsuang, 1982; Murray, 1985) which we now believe may relate to underlying lesions in different cerebral locations (Andreasen & Olsen, 1982). While Kraepelin certainly alluded to the notion of schizophrenia as a heterogeneous group of disorders, it was Bleuler who later came to emphasize the importance of examining subtypes.

Historically, researchers and clinicians, unable to agree upon a definition, have used a variety of diagnostic criteria, some very narrow, others more broad. Schizophrenia is however now recognized as a group of psychotic disorders, characterized fundamentally by gross distortions of reality, withdrawal from social interaction, disorganization of thought, fragmentation of perception and disturbance of emotion (Murray, 1985). Disorders of perception and thought are manifested in delusions, hallucinations and inappropriate or unusual behavior; whereas emotional disturbance is reflected in inappropriate affect such as undue anxiety or fearfulness. Psychomotor under- or over-activity, social withdrawal and self-neglect are usually present to some degree. Although schizophrenia often has its onset in adolescence and young adulthood (American Psychiatric Association, 1983), the course of the

illness is generally unpredictable and varies from person to person (Pfohl & Winokur, 1982). Much debate and research continue to be conducted to evaluate its central features and their most important characteristics (Hamilton, 1984).

SCHIZOPHRENIA: CURRENT CONCEPTS

Ideas about the origins of abnormal behavior in schizophrenia have undergone enormous change since Kraepelin first described the illness nearly a century ago. Psychiatric theories have moved away from speculations about the environment toward an emphasis on biological variables (Andreasen, 1984b). The early notion that the brain was somehow involved in the schizophrenic process has received widespread support in recent years. In particular, chemical (Crow, 1980; Crow, Ferrier & Johnstone, 1986) as well as structural (Averback, 1981; Golden, Graber, Coffman, Berg, Newlin et al., 1981; Andreasen, Nasrallah, Dunn, Olson, Grove, Ehrardt et al., 1986) changes in the brain have been identified, although these may be predisposing factors rather than actual causes.

To date there is no clear indication as to what causes schizophrenia. Twin studies of schizophrenia suggest (Crowe, 1982) that hereditary factors play a role, but they are not all-important. Viral infections (Torrey &

Peterson, 1976) and head-injuries (Feuchtwanger & Mayer-Gross, 1938) have also been implicated. Recognizing that schizophrenia is probably a heterogeneous group of disorders, some subtypes may be caused by one factor and some by another.

Schizophrenia is found worldwide (Murray, 1987). In Canada, incidence rates (number of new cases), based on admission data from psychiatric facilities, show a higher rate for males than for females, with a general prevalence rate of 10.36 per thousand for males and 6.76 per thousand for females (Pyke, 1986). Other figures suggest approximately 200,000 people in Canada suffer from schizophrenic illness and that at least 60,000 require long-term institutionalization (Pyke, 1986). In other words, roughly one-third require extensive support in their day-to-day lives.

There are two main interventions used today in the treatment of schizophrenia: pharmacological and psychosocial (Murray, 1986). Neuroleptic drugs such as phenothiazines (e.g., chloropromazine) have been used in the treatment of schizophrenia for many years (Julien, 1978). Psychosocial approaches include individual and group psychotherapy, skill training and community support groups. In actual practice, many patients often receive various types of intervention concurrently.

SCHIZOPHRENIA AS A BRAIN DISEASE

The role of brain dysfunction in at least a portion of schizophrenics has been suspected since Kraepelin and Bleuler first described the syndrome. Kraepelin and Bleuler were among the first to describe a variety of "soft" neurological signs in schizophrenia such as abnormal pupillary responses, altered reflexes, tics, ataxias, and petit mal seizures (Seidman, 1983). More recently the notion that the brain is pathologically involved in the schizophrenic process has been supported by investigations using various neurodiagnostic techniques (Henn & Nasrallah, 1982; Seidman, 1983; Young & Williamson, 1986). With increasingly sophisticated technology and more methodologically sound investigations, behavioral scientists are making significant advances in their understanding of those factors implicated in the etiology and outcome of the disease. What follows is a review of evidence that demonstrates neurologic abnormality, structural anomaly (pneumoencephalography, computerized axial tomography, magnetic resonance imaging), metabolic changes (positron emission tomography, regional cerebral blood flow), electrophysiological abnormality (EEG), histological changes (autopsy) and neuropsychological dysfunction in schizophrenia.

Neurological Abnormalities

In a 1982 review of neurological abnormalities associated with schizophrenia, Stevens states that from a neurological perspective the psychiatric history, mental state, neurological history, and behavior of individuals with schizophrenia reflect a constellation of symptoms and signs that directs attention to specific areas of the brain subserving these functions. Based on this inference, the search for cerebral substrates for the pathology and/or disturbed physiology underlying schizophrenic symptoms has been approached as a direct neurological problem of cerebral localization (Stevens, 1982). As with other focal brain lesions, it has been assumed that by closely observing behavior we may determine the location of the disorder.

The pathology underlying the acute psychotic stages of schizophrenic illness can be characterized by a number of bizarre sensory experiences, including unusual auditory, visual, tactile, somatosensory, and olfactory phenomena (Stevens, 1982). The standard neurological examination may reveal minor asymetrical reflexes, however the occurence of "hard" neurological signs is comparatively rare (Seidman, 1983). Instead, most schizophrenics seem to demonstrate a variety of "soft" neurological disturbances. These disturbances may include stereotypic behavior such as

posturing, blinking, stillness and, fixity of gaze as well as rubbing, rocking, pacing, muttering, and other rituals which resemble the automatisms of psychomotor epilepsy. Conversely, temporal lobe epileptics sometimes develop a "schizophrenic-like psychosis" in the chronic stage of illness which closely resembles schizophrenia (Stoudemire, Nelson & Houpt, 1983). This resemblance has led to speculation that the disturbed physiology underlying psychomotor epilepsy may also be present in schizophrenia (Taylor, 1977).

The range of perceptual disturbances, auditory, visual, olfactory, somatosensory, and visceral hallucinations, as well as a sense of fear or strangeness experienced by most schizophrenics are so frequently expressed in the auras of patients with temporal lobe epilepsy (TLE) that the involvement of underlying limbic structures in both disorders has been strongly suggested (Blumer, 1975). However, in contrast to the latter, the automatisms and stereotypies of schizophrenia can nearly always be disrupted and there is no amnesia. Thus, while some schizophrenic behaviors may resemble, at least superficially, psychomotor epilepsy, there is little if any, evidence to suggest that they are seizure related (Stevens, 1982).

While it appears unlikely that schizophrenic symptoms are ictal phenomena, the results of human and

animal studies support the notion that limbic system pathology may account for at least some symptoms of schizophrenia (Stevens, 1982). For example, it has been shown that lesions to the entorrhinal cortex and amygdala in experimental monkeys produce a disturbance in signaling behavior and interpretation of social cues leading to isolation and apathy (Kling, Lancaster & Benitone, 1970). The behavioral changes brought about by these limbic lesions has been described as "strikingly reminiscent" of the schizophrenic defect state (Stevens, 1982).

Schizophrenics also report a variety of sometimes frightening, sometimes pleasurable visceral sensations, many of which can be elicited by stimulation of amygdala, septum, thalamic and midbrain sites in humans (Nashold, Slaughter & Gills, 1969; Stevens, Mark, Ervin, Pacheco, & Suematsu, 1969). In addition, changes in sleep, appetite, menstrual and sexual patterns among early schizophrenics direct attention to the hypothalamus (Stevens, 1982). Thus, many of the altered perceptual experiences of schizophrenics may be related not only to limbic system dysfunction but to dysfunction in various subcortical areas.

Multiple motor disturbances have also been associated with schizophrenia. Catatonia, a state of waxy flexibility, often accompanied by mutism, immobility or stupor, is found in some schizophrenics. Catatonia, while

not specific to schizophrenia, has been reported in patients with viral encephalitides which attack the basal ganglia and midbrain. Since catatonic states are produced by bilateral lesions of the globus pallidus (Mettler & Crandell, 1959), catatonic schizophrenia has also been associated with neuronal loss in the globus pallidus (Stevens, 1982).

Tics are abnormal movements which are common to schizophrenia (Stevens, 1982). Even Kraepelin (1919) noted choreiform movements, particularly of the face, in his description of dementia praecox. Tics, choreiform movements and other dyskinesia provide additional evidence of extrapyramidal dysfunction.

The most consistent neurological abnormalities found in schizophrenia occur among ocular movements. Abnormalities of ocular movement include: (a) absence and/or avoidance of eye contact, including staring, (b) abnormal (i.e., decreased, increased, or paroxysmal bouts of eye blinking) blink rates, (c) abnormal glabellar reflex, (d) episodic, lateral deviation of the eyes, (e) paroxysmal saccadic eye movements, (f) interruption of smooth ocular pursuit movements, (g) inability to move the eyes independent of the head, (h) inability to converge, and, (i) pupillary inequality or dilated pupils (Stevens, 1982). While the structures responsible for eliciting these abnormal movements are poorly understood, they may

someday prove potentially useful in identifying the systems affected by the disorder.

While most investigations of neurological abnormality in schizophrenia report a significant excess of "soft" neurological signs, Kinney, Woods and Yurgelun-Todd, (1986) found an abundance of "hard" neurological signs in schizophrenics as compared to controls. Kinney and associates performed standard neurological examinations on 24 schizophrenics, 21 non-schizophrenic siblings and parents of schizophrenics and 24 normal controls. They found the prevalence of neurological abnormalities in relatives significantly greater than among controls, but similar to that among schizophrenics. This pattern of results suggests that these signs are not the consequence of psychotropic medication, but rather of some etiological process that is familial. The dissociation of psychopathology and neurological signs was taken to support the hypothesis that a combination of psychopathological and neurological factors produce schizophrenia.

In summary, neurological studies of schizophrenia suggest an excess of both soft and hard neurological signs (Heinrichs & Buchanan, 1988) although the former are more common. While many of these signs are neither diagnostic, nor specific to schizophrenia, one or more of them can be found in nearly every case of schizophrenia examined.

Pneumoencephalography (PEG)

PEG studies were among the first to demonstrate gross cerebral pathology in schizophrenia. The technique, now antiquated, involves injecting air into the subarachnoid space and cerebral ventricles where it serves as a contrast medium for conventional x-rays. Distortion of the normal appearance of the air-filled spaces is considered suggestive of pathology. Seidman (1983), in a review of the literature, tabulated 35 references to PEG in schizophrenia, most of which were published prior to 1950.

PEG studies are notoriously difficult to interpret because of non-random sampling, non-use of control subjects, unspecified diagnostic criteria, non-standardized PEG procedures and unsophisticated statistical analyses. However, despite these methodological problems, remarkably uniform results were obtained.

The majority of studies are taken to reflect structural brain abnormality in a significant proportion of schizophrenics. The most common (i.e., 35-70%) finding among schizophrenic patients is mild/moderate enlargement of the ventricles (e.g., Huber, 1957). Cortical atrophy, although less frequent (i.e., 20-35%), is also noted (e.g., Haug, 1962). While structural abnormality seems to be present in a significant portion of schizophrenics an equally important outcome of PEG research is the

observation that enlarged ventricles and/or cortical atrophy is not observed in every schizophrenic patient. Nor, when found, is it diagnostically specific. However, when present, PEG abnormalities, in general, have been associated with unfavourable prognosis (Huber, Gross & Shutter, 1975), while PEG assessed ventricular size, in particular, seems to correlate positively with degree of overall adaptive impairment (Kiev, Chapman, Guthrie & Wolfe, 1962), impairment at work and in social life (Lonnum, 1966) and decreased cognitive functioning (Matthews & Brooker, 1972).

In summary, PEG studies were among the first to establish that structural brain changes (i.e., ventricular enlargement and cortical atrophy), while not diagnostically specific, are nevertheless present in many schizophrenics. They also suggested that individuals who show these abnormalities are more severely effected and receive a poorer prognosis (Weinberger & Wyatt, 1982; Seidman, 1983).

Electroencephalography (EEG)

The EEG is an investigative technique which involves recording the electrical activity of the brain by means of electrodes placed on the scalp. The scalp electrodes are usually placed in a standardized pattern and the potential difference between points are measured, amplified and transcribed using a devise such as a pen

recorder. Early studies of EEG findings among schizophrenics tend to be plagued primarily by non-standardized EEG evaluations (Vianna, 1975) and ill-defined criteria for diagnosing schizophrenia (Pope & Lipinski, 1978). Low inter-rater reliability and failure to control for drug and ECT effects are other factors limiting the interpretation of these studies (Mirsky, 1969). Nevertheless early studies (e.g., Hill, 1952; Heath, 1954) suggest that the overall rate of EEG abnormality among schizophrenics ranged from 5-80% with an average of about 25% abnormal (Stevens, 1982; Seidman, 1983).

More recent investigations, using improved methodologies, do however provide stronger support for the earlier notion that EEG abnormalities are found more frequently among schizophrenics than among normal controls or patients suffering from other major psychiatric disorders such as depression (Abrams & Taylor, 1979) or bipolar affective disorder (Pope & Lipinski, 1978). While there seems to be no characteristic EEG abnormality that is pathognmonic of schizophrenia (Vianna, 1975; Mirsky, 1969), the rate of EEG abnormality among schizophrenics in general tends to range from 20-40% regardless of subtype, chronicity, or severity of illness, in contrast to 0-10% among normal controls (Itil, 1977) and 10-20% among affective disorders (Abrams & Taylor, 1979). Furthermore,

EEG abnormalities, when found, tend to be diffuse and non-specific, although focal temporal abnormalities appear to be the most common finding of localizing significance (Stevens, 1982; Seidman, 1983).

In an effort to reorganize spectral EEG data into a topographical representation, a newly devised system known as brain electrical activity mapping (BEAM) has also been employed in schizophrenic research. BEAM is a computer-assisted technology which organizes EEG data from multiple cerebral locations in order to produce a color-coded picture summarizing electrical activity across the cortex (Young & Williamson, 1986).

Morihisia, Duffy & Wyatt (1983) used BEAM with EEG data from 25 medicated and unmedicated schizophrenics and found consistently increased bifrontal slow activity and increased post-central fast activity. Bifrontal slowing has been replicated in other controlled studies (Morstyn, Duffy & McCarley, 1983; Guenther & Breitling, 1985), but not reliably (Williamson & Mamelak, 1987). In addition, Morihisia & McAnulty (1985) observed a correlation between increased bifrontal slow activity (BEAM) and frontal atrophy (CT).

Evoked (EP's) and event-related (ERP's) potentials are another EEG methodology which provide for examination of electrophysiological correlates of cognitive processing related to specific behavior e.g., reaction time. Auditory

(e.g., tone), visual (e.g., light flashes) and somatosensory (e.g., touch) stimulation, for example, have been used to study immediate (e.g., Herman, Mirsky, Ricks, & Gallant, 1977) and sustained (e.g., Friedman, Vaughan & Erlenmeyer-Kimling, 1975) attention both in schizophrenia and in populations at risk for schizophrenia.

In a review of recent EP/ERP literature in schizophrenia, Holzman (1987) noted that, generally speaking, chronic schizophrenics show diminished variation and shorter latencies of early components of brain potentials, a finding he interprets as indicating impaired modulation of stumulus input resulting in too much information reaching cortical areas. In addition, schizophrenic patients seem to show reduced amplitudes of later components of brain potentials interpreted as reflecting impaired selective attention (Holzman, 1987). Laterality differences, in which the left hemisphere is less efficient than the right, have also been reported (Roemer, Shagass, Straumanis & Amadeo, 1978; Buchsbaum, 1979).

Findings with respect to ERP's among populations at risk for schizophrenia have been less reliable. In a review of EEG data on children of schizophrenic parents, Erlenmeyer-Kimling et al., (1982) concluded that there was sufficient inconsistency among published studies that further research was recommended. However, observations of

reduced amplitude in late ERP components, one of the most consistent findings in chronic schizophrenia, was found in at least two independent samples of high risk children (Friedman, Vaughan, & Erlenmeyer-Kimling, 1980; Friedman, Erlenmeyer-Kimling & Vaughan, 1982), providing at least some support for the hypothesis of attentional deficits and impaired cognitive processing in schizophrenia.

In summary, conventional EEG studies in schizophrenia (spectral analyses) demonstrate a variety of significant but nonspecific changes in brain electrical activity compared to normals. Efforts to localize these changes are limited by the small number of electrode sites and difficulties interpreting the enormous amount of data generated by computer-assisted analyses of EEG information. The organization of EEG information into topographical maps (i.e., BEAM), has however helped to elucidate regional differences in brain electrical activity between schizophrenics and normals. In particular, bifrontal slowing appears to be a reproducable finding, a finding which may correlate well with frontal abnormalities found in CT and rCFB studies, which follow. In addition, evoked-potential data provide tentative support for impaired registration and processing of sensory-perceptual information in schizophrenia, moreso in the left than right hemisphere of the brain. Lateralized and/or greater left hemisphere dysfunction has been reported in some

neuropsychological studies, which also follow.

Computerized Tomography (CT)

Simply put, the CT scan is an electron imaging devise which produces tomograms, or x-rays, of selected layers of the body, including the brain. In fundamental terms, a co-efficient of radiation absorption (based on several hundred x-ray transmissions) is calculated, by computer, to produce a composite picture (Ontario Council of Health, 1980). Other names for the technology, which have been used interchangably, include Computerized Transverse Tomograpahy (CTT) and Computer Assisted Tomography (CAT).

The measurements which have been utilized in CT studies among schizophrenic populations can be broadly classified into three categories: (a) linear measurements (i.e., maximum distance between lateral tips of the anterior horn of the lateral ventricles) (e.g., Weinberger, Torrey, Neophytides & Wyatt, 1979a), (b) area measurements (ventricular brain ratio's; VBR's), using planimetry or computerized programs which take advantage of the tomographic characteristics of CT scanners (e.g., Shelton et al., 1988), and, (c) volumetric measurements, generally of a tentative and experimental nature (e.g., Jernigan, Zatz, Moses & Berger, 1982). These measures are generally aimed at providing objective evidence of structural and/or

volumetric changes of CSF-filled spaces as well as assessment of asymmetry. No one type of measure is more widely accepted than another and an appreciation of each category is fundamental in order to interpret CT findings. Several major reviews of CT scanning and schizophrenia have been published (e.g., Dennert & Andreasen, 1983; Goetz & van Kamme, 1986; Seidman, 1983; Weinberger & Wyatt, 1982) in the psychiatric literature.

CT studies of schizophrenia have proven to be methodologically superior to earlier PEG and EEG studies and are credited for having adopted stringent criteria for psychiatric diagnosis. In addition, the CT has enjoyed immense popularity largely because it is non-invasive and does not carry with it the pain or discomfort of earlier neurodiagnostic techniques.

Research on CT abnormalities in schizophrenia appear to focus on five main areas: ventricular enlargement (e.g., Reveley, 1985), cortical atrophy/sulcal enlargement (e.g., Dewan et al., 1986), changes in brain density (e.g., Golden et al., 1981), cerebellar atrophy (e.g., Weinberger, Torrey & Wyatt 1979), and reversed cerebral asymmetry (e.g., Jernigan et al., 1982).

Ventricular enlargement is one of the most common CT findings among schizophrenics (e.g., Obiols, Marcos & Salamero, 1987). Johnstone, Crow, Frith, Husband and Crow (1976) reported the first CT study of schizophrenics,

observing enlarged lateral ventricles in more than 50% of their group with chronic schizophrenia. Since that time, lateral ventricular enlargement has been found (e.g., Weinberger, Torrey, Neophytides & Wyatt 1979a) in the majority of investigations with the prevalence of ventricular enlargement ranging from 6% (Andreasen, Smith et al., 1982) to 60% (Golden et al., 1980). There have also been studies showing enlargement of the third (Bankier, 1985) and fourth (Dewan et al., 1986) ventricles of chronic schizophrenics relative to controls. In addition, ventricular enlargement has been variously associated with poor response to treatment (Weinberger, Cannon-Spoor, Potkin & Wyatt, 1980), poor prognosis (Williams, Reveley, Lolowshi, Arden & Mandelbrote, 1985), poor premorbid adjustment (Weinberger et al., 1980), neuropsychological impairment (Donnelly, Weinberger, Waldman & Wyatt, 1980), length of illness (Moriguchi, 1981) and negative symptoms (Andreasen & Olsen, 1982).

Some studies have not found ventricular enlargement. Negative findings, however, have been generally dismissed owing to (a) clinical differences in schizophrenic samples (Luchins, 1982) and (b) inadequate procedures for quantifying ventricular size. For example, investigations of ventricular enlargement in schizophrenia along the acute/chronic dimension demonstrate that enlarged ventricles are more common among the latter group (Dennert

& Andreasen, 1983). Failure to find ventricular enlargement is therefore more common among studies using relatively young or acute schizophrenic patients.

In an effort to address the question of methodological problems, Reveley (1985) examined the reliability of five common measures of ventricular size. He concluded that when careful, blind measurements are made by a trained observer, and when the CT scans of patients and age-matched controls are made on the same scanner (and examined at the same time) all methods reliably distinguish schizophrenics with enlarged ventricles from controls at approximately the same level of significance. His findings support the position that measurement problems may contribute to the failure to find ventricular enlargement in some patients. Reveley also noted that the ventricular brain ratio's (VBR's; a ratio of ventricular area to brain area expressed as a percent) of schizophrenic patients tended to fall into a bimodal distribution, supporting the position that enlarged ventricles are not a characteristic of all schizophrenics but rather of a subgroup. Current studies now focus on factors which characterize that subgroup of schizophrenics in which enlarged ventricles and other associated brain abnormalities can be detected.

Findings of cortical atrophy have also been reported in the schizophrenia literature. However, owing to even greater measurement problems, studies of cortical

atrophy (i.e., sulcal enlargement) are somewhat more difficult to interpret. Nevertheless sulcal enlargement when found, like ventricular enlargement, has been associated with cognitive impairment (Rieder, Donnelly, Herdt & Waldman, 1979). Interestingly, patients who have sulcal enlargement tend not to have enlarged ventricles and vice versa (Dennert & Andreasen, 1983; Dewan et al., 1986). These patterns of findings has been interpreted as evidence for at least two different types of pathological processes occurring in schizophrenia. For example, ventricular enlargement may reflect atrophy of deep (i.e., subcortical) brain structures while sulcal enlargement may reflect diffuse cortical atrophy (Dennert & Andreasen, 1983). The repeated lack of association between indicies of ventricular enlargement (i.e., VBR's) and sulcal enlargement has fueled speculation about two different subgroups of schizophrenics with independent etiological factors (Dewan et al., 1986).

Brain density changes in schizophrenia have also been reported although, again, the literature is difficult to interpret as the methods and areas used to measure CT density varies markedly between studies. In general, some studies (Golden et al., 1981) have found, relative to controls, significant changes in brain density while others (Dewan et al., 1986) have not. Among studies with positive findings, some report decreased (Golden et al., 1981) while

others report increased (Largen et al., 1984) brain density in some regions.

Golden et al., (1981) examined brain density in schizophrenia and found, specifically, decreased density throughout the left hemisphere as well as lower density in the anterior right hemisphere when compared to brain density numbers from normal control subjects of the same age. In contrast, Largen et al, 1984 found increased density in the right but not the left hemisphere relative to controls. Dewan et al., (1986), pursuing the possibility that a subgroup of schizophrenics were responsible for marginally significant density changes in whole-group comparisons, compared density measures of schizophrenics with enlarged lateral ventricles to those with normal CT's. In the group with enlarged ventricles, all lobes except the temporal lobes were "either significantly more dense or showed a strong trend in that direction" (p. 158-159). Dewan and associates speculated that "fibrillary gliosis" was the most likely explanation for hypodensity although increased mineral or heavy metal deposits in the brain were also possible etiological factors. These authors cited neuropathological evidence of increased gliosis as well as iron and calcium masses in schizophrenic brains to support their hypothesis. On the other hand, hyperdensity, when found, has been attributed to a genetic disorder or some disease process that might

inhibit proper neuronal development including inadequate nutrition, birth trauma and/or other perinatal or childhood factors (Golden et al., 1981). To date, the number of studies examining brain density is modest and positive findings have not been well replicated. Regardless of whether density measurements reveal regions of hyper- or hypo-density most studies emphasize the need to identify definable subgroups of schizophrenics for whom these changes may have clinical significance.

Cerebellar atrophy has also been observed in the CT scans of some schizophrenic patients (Heath, Franklyn & Shraberg, 1979; Weinberger et al., 1980; Weinberger, Torrey & Wyatt, 1979; Nasrallah, Jacoby & McCalley-Whitters, 1981). Weinberger et al. (1979) evaluated, by CT, 60 patients diagnosed with chronic schizophrenia. While most patients were found to have ventricular enlargement as hypothesized, an incidental finding of cerebellar atrophy was observed in a subgroup of ten schizophrenics. Since cerebellar atrophy is common among chronic alcoholics, the data from one patient with a history of alcohol abuse, was excluded from further analysis. The remaining scans were found to show definite atrophy of the vermis and in one patient the cerebellar hemispheres were also considered atrophied. In a follow-up investigation, Weinberger et al. (1980) conducted a "morphometric" study which verified CT evidence of structural abnormality in the cerebellar

vermis. The atrophy was also found to be most marked in the region of the anterior cerebellar vermis. Weinberger et al. (1980) speculate that the significance of gross cerebellar atrophy lies in the fact that the cerebellar vermis is linked, anatomically and functionally, to areas of the limbic system that have been implicated in schizophrenia. Observations such as increased dopamine in the limbic forebrain (a neurochemical abnormality consistent with the "dopamine hypothesis" of schizophrenia) produced in the rat by a lesion of the vermis suggest that abnormalities of the cerebellar vermis may be related to the pathogenesis of some schizophrenic symptomatology (Weinberger et al., 1980). Interestingly, schizophrenics who show atrophy of the cerebellar vermis tend to be a different group than those displaying ventricular enlargement (Dennert & Andreasen, 1983), suggesting that those who exhibit cerebellar atrophy may represent a subgroup distinct from those who exhibit enlarged ventricles.

In a recent review of neuroradiological studies of cerebellar pathology in schizophrenia, Lohr & Jeste (1986) pooled data from 18 investigations and found 18% of all CT scans were suggestive of cerebellar atrophy compared to only 4% among normal controls. It would seem that while cerebellar pathology may characterize a subgroup of schizophrenics, clinical definition of such a subgroup has

not yet been accomplished. Thus despite much speculation, the significance of cerebellar atrophy in schizophrenia is unclear.

The majority of CT abnormalities reported thus far consist of pathologies which are primarily diffuse or bilateral in nature. Other studies (Luchin, Weinberger & Wyatt, 1979) have focused on and revealed patterns of unusual asymmetry (i.e., reversal or absence of typical patterns) in brain structure. Studies of structural asymmetry principally test the hypothesis that schizophrenia is a left hemisphere disease.

The idea that schizophrenic symptoms may be related to left hemisphere dysfunction comes from clinical observations of disturbed verbal behavior, the seemingly high incidence of pathological left-handedness (i.e., no genetic history of sinistry) and the preponderance of schizophrenic-like psychoses among epileptics with a left-sided focus. To date, the result of these studies are conflicting in that some investigators have found diffferences while others have not.

Structural asymmetries frequently found in the brains of normal right-handed individuals by CT, include wider right relative to left frontal lobes and wider left relative to right occipital lobes. Luchins et al., (1979) examined CT scans of 57 right-handed schizophrenics and found reversed frontal and occipital asymmetry in 33 and 25

percent respectively. This reversal was correlated with a lack of evidence of cortical atrophy as measured by ventricular enlargement. Naeser et al., (1981) identified a subgroup of right-handed, leucotomized schizophrenics with a reversal of occipital width asymmetry. These studies have been criticized, however, for failing to take into account the frequently encountered deviation of the straight sinus to the right, probably resulting in an overestimate of right occipital width (Dennert & Andreasen, 1983). In contrast, Andreasen et al. (1982) did take straight sinus deviation into account and failed to find significant reversal of asymmetry in their sample of 43 right-handed schizophrenics. Other more recent studies have also failed to find reversed cerebral asymmetry (e.g., Jernigan et al., 1982). While many of these studies use linear measurements to determine asymmetry, Golden et al. (1981) measured sulcal enlargement by planimetry and found significantly more atrophy in the left frontal lobe than in other brain regions. The lack of uniform findings among relatively few studies strongly suggests that additional study in this area is needed before even tentative conclusions can be drawn. However, even if reversed cerebral asymmetry can be reliably demonstrated in a subgroup of schizophrenics the significance of this finding is unclear, except to say that reversal of normal asymmetry is frequently associated with various disorders of higher

cortical functioning (e.g., autism, delayed speech onset and developmental dyslexia) (Luchins et al., 1979).

In summary, the preponderance of CT evidence suggests that there exists a subgroup of schizophrenics with significantly larger ventricles. There is further evidence to suggest that this same subgroup may share other characteristics such as negative symptoms, a poor prognosis and neuropsychological deficits. In addition, a relatively modest number of studies have found sulcal enlargement, cerebellar atrophy, brain density changes or reversed cerebral asymmetry in other schizophrenics although the clinicopathological correlates of these abnormalities remain largely unexplored.

Regional Cerebral Blood Flow (rCBF)

Using radioactive xenon gas as a tracer of cerebral blood flow the functional activity of the brain can be assessed by directly measuring cerebral glucose metabolism both at rest as well as during periods of cognitive stimulation.

In a 1983 review of rCBF studies comparing schizophrenics to normal controls, Seidman concluded that rCBF at rest is frequently reported as hypofrontal with postcentral flow relatively high according to anterior/posterior comparisons. Since total mean hemispheric flow for most schizophrenics is usually within

normal limits (Buchsbaum, Ingvar et al., 1982), the pattern suggests an abnormal distribution of (cortical) function in schizophrenia. Although the theoretical significance of hypofrontality in schizophrenia is unclear, Ingvar (1976) notes that, clinically, maldistribution of flow is typically associated with more autistic, mute and withdrawn behavior, especially in older, more chronic schizophrenics.

The pattern of hypofrontality has also been observed during cognitive stimulation. Weinberger, Berman & Zec (1986) evaluated rCBF in 20 unmedicated schizophrenics and 25 controls, first at rest then while performing an abstract reasoning and problem solving task (Wisconsin Card Sorting Task; WCST). During rest, schizophrenic patients showed significantly reduced relative but not absolute rCBF as expected. While performing the WCST both absolute and relative rCBF significantly discriminated schizophrenics from controls. In addition, abnormal patterns of rCBF correlated with cognitive impairment. These findings were taken as support for the position that schizophrenics who show abnormal paterns of CFB with associated cognitive impairment have a diminished capacity to increase frontal metabolism even when there is a specific need for it (Weinberger et al., 1986).

While the majority of rCBF studies (eg. Mathew et al., 1981) report a hypofrontal response among

schizophrenics, others have noted a more lateralized decrease in metabolic rate. For example, Ingvar (1976) found a significant reduction in left frontal regions, whereas Mathew et al. (1981) found slightly lower right frontal activation. While the local reduction of flow in frontal regions is a fairly uniform finding in schizophrenia, studies which report asymmetric reductions have been inconsistent.

It is also apparent from the data that not every schizophrenic shows the same pattern of hypofrontality, or at least some seem to show it more than others. Assuming that rCBF anomaly reflects brain disease, it has been postulated that abnormal metabolism may reflect a subtle structural lesion of the frontal regions affecting its dopaminergic innervation (Weinberger & Berman et al., 1986) with associated pathologic changes in limbic and diencephalic nuclei, given that the prefrontal cortex is anatomically linked to these regions. CBF studies, therefore, seem to tie in with longstanding theories of schizophrenia which have stressed frontal lobe and limbic dysfunction. Kraepelin and Bleuler, for example, both implicated the frontal lobes as a possible locus for the pathologic changes in schizophrenia.

More recently it has also been suggested that frontal lobe dysfunction is not only of pathogenic significance but also helps explain some of the clinical

symptoms associated with schizophrenia. Invgar (1976) was among the first to report that schizophrenics who have lower frontal rCBF tend also to be the most withdrawn, mute and indifferent. His linking of abnormal rCBF patterns to negative symptoms of schizophrenia is relevant to an emerging body of evidence which suggests that subtyping according to the positive/negative symptom distinction may be of great practical as well as theoretical significance (Andreasen & Olsen, 1982).

In summary, CBF studies support the notion that some schizophrenics show evidence of decreased metabolic and, by inference, functional activity of the frontal lobes. Furthermore, this anomaly, when found, has been associated with negative symptoms and defect states. While the hypofrontal pattern among schizophrenics stands in contrast to the hyperfrontal pattern seen among normals and the pattern of reduced mean CBF seen in patients with dementia (e.g., Alzheimer's Disease) (Seidman, 1983) a similar pattern has been observed among depressed patients (Mathew et al., 1980). These findings suggest that hypofrontality may be associated with, but not specific to, schizophrenia.

Positron Emission Tomography (PET)

Local glucose metabolism has also been measured by PET. PET scanning works in a manner similar to rCBF and CT

scanning. Radioactive substances (i.e., 15-Oxygen, 11-Carbon, 15-Florine) are injected into a blood vessel and radiation emitted from those brain regions which are most active, is measured by detectors which surround the head (Cohen, Semple & Gross, 1986).

Most PET studies (Farkas et al., 1980; Buchsbaum et al., 1982), like CBF data, report lower frontal activation in schizophrenics relative to normals (Seidman, 1983). In addition to findings of decreased frontal activation in schizophrenia (e.g., Buchsbaum et al., 1981), other abnormalities include incidental findings of hemispheric asymmetry of cerebral metabolism (Buchsbaum et al., 1981), as well as decreased metabolic activity among subcortical structures (Farkas et al., 1980).

Among researchers pursuing the hypofrontality hypothesis laid down by earlier rCBF investigations, Buchsbaum et al, (1982) found a pattern of low activation among eleven young, unmedicated schizophrenics in both the superior frontal pre-motor areas and caudate nuclei of the basal ganglia, areas generally believed to play a role in motor programming and goal-directed motor behavior. A similar pattern was reported by Farkas et al. (1980) and Widen, Bergstron & Blomquist, (1983). In addition, Farkas et al. (1980) found decreased activity in the lenticular nucleus, thalamus, and cingulate gyrus. These data have since given rise to the hypothesis that schizophrenics may

suffer from a fundamental deficit in frontal activation due to a defect in the cortico-subcortico dopaminergic system resulting in a failure of brain stem and limbic mechanisms to activate the frontal lobes (Buchsbaum et al., 1982; Seidman, 1983). Such a system, although implicated, is not well delineated neuroanatomically.

One criticism of both CBF and PET studies has been that data are typically collected while the subject is in a state of relaxation and that during this resting state the subject's mental experience and corresponding physiologic characteristics are poorly controlled (Weinberger et al., 1986). Taking a cue from studies which had demonstrated the capacity of pain to increase CBF to the frontal cortex Bauchsbaum et al., (1984) used this form of somatosensory stimulation to better control the psychological state of the patient. As in an earlier 1982 study, the same pattern of hypofrontality was seen, however, only in the right hemisphere. While his findings stress the importance of controlling mental activity, they detract from the general finding of global hypofrontality in schizophrenia.

Other studies have failed to support the hypofrontality hypothesis altogether. Widen et al., (1983) used the temporal lobes as a point of reference rather than the usual parietal-occipital regions as the basis for frontal comparisons and found a normal anterior-posterior ratio in a sample of 12 schizophrenic and 4 controls. Thus,

the choice of cortical region for standardization appears to have some bearing on the presence or absence of hypofrontality.

In a recent investigation, Szechtman et al. (1988) examined the effect of antipsychotic medication on cerebral metabolic activity, as measured by PET, in two groups of schizophrenic patients. One group was scanned before receiving their first ever dose of antipsychotic medication and again after having been treated pharmacologically for one year. The second group had been medicated for four to fourteen years. Their data served to demonstrate that exposure to neuroleptics alters the profile of regional glucose metabolism. The Szechtman et al. (1988) study is significant in that it is the first study to report enhanced metabolic activity in the frontal lobes (hyperfrontality) along with diminished activity in posterior cortical areas among never-medicated, acute schizophrenics relative to normal subjects. While one year of medication did not significantly alter the schizophrenic metabolic profile (with the exception of increased glucose metabolism in the corpus striatum), attenuation of the schizophrenic pattern of frontal hyperactivity and posterior hypoactivity was observed over the four to fourteen year period of exposure to neuroleptic medication resulting in a generalized "posterior shifting" of cortical activity toward normalized values. While these finding may

explain patterns of hypofrontality reported elsewhere (Farkas et al., 1980) on the basis of prolonged exposure to antipsychotic medication, they contrast with the pattern of hypofrontality reported by Buchsbaum et al. (1982) in their sample of unmedicated schizophrenics. It is of interest that Szechtman et al., (1988) also introduce the concept of "cerebral metabolic tone" (defined as the intrinsic cortical activity observed during periods of noncognitive stimulation) and suggest that altered cerebral tonus may account for some symptoms of schizophrenia.

Based on a review of PET studies in schizophrenia, Cohen et al. (1986) was unable to reach a definite conclusion regarding the hypofrontality hypothesis and suggest that the interpretation of existing data as evidence of a decrease in frontal activity, and therefore "executive functions", is presently unwarranted by implication. Recent studies (Szechtman et al., 1988) also continue to challenge earlier findings of purported hypofrontality in schizophrenia. In addition, hemispheric laterality differences, more frequently found in studies reporting relative hypofrontality, are also inconsistent and therefore inconclusive. The significance of other regional disturbances, including reports of significantly reduced metabolism in the parietal lobe, hippocampus, temporal lobe, the septal region, the limbic system including the corpus striatum and nucleus accumbens, basal

ganglia, and the reticular activating system (Cohen et al., 1986) in the PET literature, also remain unclear.

In summary, PET data have provided less support for hypofrontal metabolic activity in the brains of schizophrenics than rCBF studies, although the results are still tentative because sample sizes have been small. Further research comparing schizophrenics to other psychiatric populations is also necessary to determine the specificity of positive findings as altered cerebral metabolism has also been reported in depression (Buchsbaum et al., 1984) and mania (Farkas et al., 1980). In addition, the relationship between regional metabolic disturbance and structural changes on CT is at present uncertain (Buchsbaum et al., 1982).

Magnetic Resonance Imaging (MRI)

MRI is a technique which uses radio waves to produce high resolution images of the brain. In fundamental terms, MRI is accomplished by placing the patient inside a huge circular magnet which causes atoms (e.g., hydrogen) in the body to align with it's electromagnetic field. When the force is turned off, the atoms revert back to their original state and in the process produce an electromagnetic signal that is fed into a computer, which in turn generates a picture of brain tissue (Kaufman, Crooks & Margulis, 1982). One advantage

of MRI is that, unlike CT images which provide visualization of transverse planes, MRI also provides visualization of saggital and coronal planes.

Like rCBF and PET studies MRI has also been used to study hypothesized frontal system dysfunction in schizophrenia. However, because MRI is a relatively new technology to behavioral scientists, few MRI studies of schizophrenia have been published in the literature.

Andreasen and Nasrallah et al. (1986) were the first to use MRI to look for specific structural abnormalities. Andreasen and colleagues studied 38, predominantly male, young, noninstitutionalized schizophrenics and 49 controls according to various brain measures, predominance of negative symptoms and performance on a battery of neuropsychological tests. They found, among males, nearly 40% had significantly smaller frontal lobes, independent of body and cranial size, particularly in the dorsolateral and orbital regions. However, contrary to expectation, decreased frontal size did not correlate with negative symptoms, such as alogia, avolition and apathy, frequently explained on the basis of frontal system abnormality. Neither was a relationship between frontal size and performance on tests tapping frontal functions found. Andreasen and Nasrallah et al. (1986) concluded that "patients suffering from schizophrenia may have had some type of early developmental abnormality that led to

impaired capacity of the brain to grow, thereby causing a correspondingly small cranial area" (p. 142). They postulated that this could be due to a variety of factors such as genetics, maternal nutrition, difficulties during delivery or environmental factors (e.g., infections). These findings, while somewhat consistent with CT evidence of cerebral atrophy reported earlier, are inconsistant with more general notions that structural abnormalities account for major phenomenologic indices of at least some schizophrenics, namely, negative symptoms and cognitive impairment.

MRI has also been used to investigate proposed increased thickness of the corpus callosum (CC) in schizophrenia. Studies (DeMeyer et al., 1988; Rosenthal & Bigelow, 1972; Rossi, Stratta, Gallucci, Passarello & Casacchia, 1988) which report a significant increase in the thickness of the CC in post-mortem brains of schizophrenics have been taken as evidence of impairment in callosal structure and interhemispheric communication.

On the basis of reported sex- and handedness-related differences in a post-mortem study of collosal dimensions in a normal population (Witelson, 1983) the effects of sex and handedness on CC thickness has also beem examined in relation to schizophrenia. Nasrallah, Andreasen et al. (1986) scanned 38 chronic schizophrenic subjects along the midline saggital plane in an effort to

obtain an optimal view of the CC. Consistent with other post-mortem findings (Rossi et al., 1988), their data also supported thicker CC in a mixed sample of schizophrenics, although further data analyses revealed that right-handed female schizophrenics accounted for most of the variance. While their data strongly suggest that increased collosal thickness in schizophrenia may be gender specific, the relevance of increased collosal size in females to schizophrenic symptoms is unknown.

In conclusion, these studies reflect only preliminary findings from a new technology which is likely to have greater impact in the mental health field as its usage becomes more widespread. These early results do, however, provide further support for the mounting evidence that schizophrenics do have some sort of structural brain abnormality and that this abnormality is of probable functional significance.

Neurohistological Studies

Despite extensive gross and microscopic scrutiny, no reliable pathological findings appear to have emerged from autopsy studies of schizophrenic patients prior to 1960 (Seidman, 1983). While cell loss in schizophrenia was reported as early as 1897 by Alzheimer, these early histological findings tend to be highly subjective and

therefore limited in their interpretation. Among quantitative neuropathological studies the most frequently reported abnormalities are a decrease in cortical cells, a decrease in the number of nerve fibers, and lipidosis (Weinstein, 1954). Other neuropathological findings include reports of changes in oligodendroglial, astrocytic and microglial elements of nerve cells, degenerative glial changes, changes in vascular and perivascular structure, cell disease and cellular sclerosis, focal demyelination, rheumatic foci, inclusion bodies, lipid increase in the nerve cells of medial thalamic nuclei, atrophy of the anterior cerebellar vermis and a significantly wider corpus callosum (Stevens, 1982). However, even these findings are of doubtful significance as they are non-specific and frequently reported in the brains of otherwise healthy, non-schizophrenics (e.g., war victims) (Tatetsu, 1964).

This lack of specificity eventually led to a widely held notion that reliable neuropathological changes do not occur in schizophrenia. Neuropathological changes, when present were then generally attributed to extraneous factors such as diet, institutionalization and treatment (i.e., psychotropic medication and the effects of ECT).

More recently, positive findings reported in CT studies of schizophrenia has led to renewed interest into the neuropathological substrata of schizophrenia. Crow (1980) compared post-mortem findings for 50 schizophrenics

with their premorbid symptom picture and found many could be classified, dichotomously, according to the presence/absence of neuropathological findings. In addition, flat affect, apathy, withdrawal and other "negative" symptoms (defect states) were related to cell loss and gross changes in brain structure, while "positive" (florid) symptoms such as hallucinations and delusions were associated with increased numbers of dopamine (DA) receptors in the brain (Crow, 1980).

Testing the hypothesis that the anatomical substrate of schizophrenia may be related to the DA receiving regions of the limbic forebrain and their projections, Stevens (1983) examined histological sections from 31 schizophrenics and identified 5 general categories of pathology not found in age-matched controls: (1) Cell (neuronal) loss, (2) beading or loss of myelin, (3) gliosis, particularly an increase in the number of astrocytes, (4) abnormal infiltration of the corpora amylacea, and, (5) granular ependymitis in the region of the ventricles. The specific pathology she described included gliotic and degenerative changes that were maximum in the regions of, including pathways in between, amygdala and basal forebrain, hypothalamus, globus pallidus, medial thalamus and midbrain and related subcortical nuclei of the limbic system. Her findings were taken as support for the hypothesis that the pathological substrata of schizophrenia

lies in related subcortical nuclei of the limbic system where 85 to 95% of all DA axons terminate (Stevens, 1982).

Histological evidence of changes in limbic regions where DA receptors are present provide support for biochemically-based theories of schizophrenia. The "dopamine hypothesis of schizophrenia," for example, holds that schizophrenic symptoms are at least partly due to hyperactivity of DA in regions of the brain which use DA as a neurotransmitter (McKenna, 1987). Other support for the hypothesis comes from pharmacological evidence that symptoms of schizophrenia can be alleviated by drugs which block DA receptors and, conversely, drugs that stimulate these DA receptors (e.g., amphetamines) produce a condition which is indistinguishable from paranoid schizophrenia (Hamilton, 1984). In fact, amphetamine-induced psychosis is, at present, one of the best available models of acute schizophrenia (Julien, 1978).

In summary, histological studies provide support for a substrata of limbic system pathology in schizophrenia. However, as histological studies of autopsy material need always contend with the problem of uncertain chemical and morphological changes following death, positive autopsy findings may not always correspond to positive findings during life and vice versa. For this reason, histological studies are likely to give way to newer technologies (e.g., MRI) which allow in vivo

examination of living brain tissue.

Neuropsychological Studies

Neuropsychological tests have also been used to assess brain damage in schizophrenia. The clinical use of neuropsychological tests is supported by early studies (Halstead, 1948) which show they reliably discriminate brain damaged from non-brain damaged persons. In fact, a large body of literature has been amassed which supports their ability to reliably discriminate between neurological patients and normal controls (Reitan & Wolfson, 1986). In contrast, neuropsychological tests may fail to discriminate adequately between patients with "functional" and "organic" disorders, particularly when schizophrenics were included in the functional group (Heaton, Baade & Johnson, 1978). Similarly, performance of patients with minor head injuries on neuropsychological tests can be very difficult, if not impossible, to distinguish from chronic, institutionalized schizophrenic patients (Watson, Thomson, Anderson & Felling, 1968; Newlin, 1983). At one time, the failure of neuropsychological tests to discriminate between organic patients and schizophrenics was considered a limitation of the neuropsychological approach.

Addressing the question of whether neuropsychological tests discriminate between brain damaged and non-organic psychiatric disorders, Heaton et al.

(1978) reviewed 94 studies that compared test scores of psychiatric patients with scores of brain damaged patients. Despite purported methodological deficiencies and inconsistencies across studies, they found most psychiatric groups other than schizophrenics performed better than organics on testing. At a time when schizophrenia was considered a functional psychiatric disorder poor performance on cognitive and perceptual tasks was generally explained on the basis of poor motivation, distractibility due to psychotic thinking (Fredricks & Finkel, 1978), the negative effects of chronic institutionalization or the effects of somatic treatment (Klonoff, Fibiger & Hutton, 1970) rather than on the basis of intrinsic brain factors (Seidman, 1983).

It is now widely recognized that neuropsychological tests fail to discriminate between schizophrenic and organic patients because a significant proportion of schizophrenics are organic (Heaton et al., 1978) and that both intrinsic and extrinsic factors contribute to cognitive deficiency in schizophrenia. By the early 1980's the idea that schizophrenics have neuropsychological deficits was widely recognized (Goldstein, 1986) and a number of neuropsychological instruments, most commonly the Halstead-Reitan Neuropsychological Test Battery (HRB) (Reitan & Davison, 1975; Reitan & Wolfson, 1985) and the somewhat more controversial (Spiers, 1981) Luria-Nebraska

Neuropsychological Battery (LNNB; Golden, Hammeke & Purisch, 1978), have been used to assess brain damage in schizophrenia.

Clinical neuropsychological investigations of schizophrenia generally involve four types of study: (a) level versus pattern of neuropsychological performance comparisons between schizophrenic and brain-damaged patients, (b) level and pattern analyses comparing subtypes (e.g., acute versus chronic) within the schizophrenic realm, (c) exploring the relationship between neurodiagnostic (e.g., CT scan) abnormalities and neuropsychological performance, and, (d) longitudinal studies of cognitive functioning in schizophrenia. In addition, experimental neuropsychology paradigms have been used to test specific cerebral laterality hypotheses.

Several extensive reviews comparing neuropsychological test performance of schizophrenics and brain-damaged groups have been published (Goldstein, 1978; Heaton et al., 1978; Malec, 1978; Seidman, 1983). The results of level-of-performance comparisons strongly support the position that many schizophrenics obtain neuropsychological test scores which fall within the impaired range and in many cases are not readily differentiated from patients with known cerebral lesions. This failure to reliably differentiate schizophrenic from organic groups on the basis of absolute test scores led

researchers to examine test profiles for patterns of deficit which may be specific to schizophrenia.

Deficit pattern analyses, using various measures from the Halstead-Reitan Battery, among schizophrenics and diffusely brain-damaged patients have generally failed to identify any characteristic pattern of cognitive dysfunction (Chelune, Heaton, Lehman & Robinson, 1979), leading to the general conclusion that the HRB does not generate performance patterns that can discriminate effectively between schizophrenic and brain-damaged patients (Goldstein, 1986). In contrast, studies using the LNNB have reported that Luria's procedures discriminate effectively between chronic schizophrenic and brain-damaged patients on the basis of profile analyses. For example, Purisch, Golden and Hammeke (1978), using 14 summary measures, were able to correctly classify 88% of their patients on the basis of all but four measures. Based on the pattern of patient performance, they concluded that brain injury seems to produce deficits on both simple and complex tasks while schizophrenia only produces deficits on complex conceptual tasks.

Numerous studies (e.g., Parsons & Klein, 1970) have attested to the difficulties schizophrenics have with conceptual tasks, particularly those which demand complex information processing, maintenance of attention, and exercise of rapid psychomotor speed (Goldstein, 1986). The

identification of conceptual deficits in schizophrenia has led some researchers to speculate, not surprisingly, that frontal lobe dysfunction may be responsible for some of the symptoms of schizophrenia. Goldstein (1986) observes that, clinically, "we tend to relate the cognition of the schizophrenic to that of the patient with a frontal lobe lesion in regard to abstraction, planning, regulation of behavior and judgement" (p. 158). PET and rCBF studies supporting "hypofrontality" have also spurred interest in frontal dysfunction. However, despite the observation that many schizophrenics demonstrate some of the behaviors seen in patients with frontal lobe lesions there is no compelling evidence to suggest that the frontal lobes are the anatomical locus of schizophrenia. Arousal and attentional deficits hypothesized to be the basis for other schizophrenic symptoms (Walker & Harvey, 1986), suggest that malfunction of the ascending reticular activating system could also be a fundamental deficit (Seidman, 1983).

Many studies (e.g., Heaton et al., 1978) support the position that chronic or process schizophrenics suffer from cerebral dysfunction because they perform as poorly as many diffusely brain injured patients and, in many cases, their performance cannot be reliably differentiated from them. However, following a major review of neuropsychological studies of schizophrenia, Heaton et al. (1978) noted that in 14 studies acute (or reactive)

schizophrenics were discriminated from brain damaged patients with a 77% accuracy rate compared to 34 studies in which chronic (or process) schizophrenics were distinguished from brain damaged patients on average at a rate of 54%. Their observations strongly suggest that chronic schizophrenics are more likely to manifest neuropsychological impairment relative to acute schizophrenics.

In summary, early neuropsychological studies of schizophrenia were initially conceptualized as a failure for their inability to adequately discriminate brain damaged from schizophrenic patients. However, the repeated confirmation of the null hypothesis (i.e., inability to reliably differentiate neurologic from schizophrenic patients on tests with known sensitivity to organic brain dysfunction) eventually lead to the alternative hypothesis that brain damage, or at least neuropsychological impairment, is a critical component of the diagnostic entity of schizophrenia. More recently, the relationship between neuropsychological (behavior) and neuropathological (brain) evidence of dysfunction in schizophrenia has received much research attention.

The relationship between neuropsychological test performance and CT findings has received substantial research attention and at least 3 major reviews have been published in this area (Seidman, 1983; Weinberger, 1984;

Zec & Weinberger, 1986). The literature reviewed here is limited to those studies using comprehensive neuropsychological batteries (LNNB, HRB) and excludes studies which employed limited screening instruments for assessing cognitive impairment.

Among researchers using the LNNB, Golden, Moses et al. (1980) examined the relationship between ventricular size and neuropsychological performance in 42 chronic schizophrenics and found ventricular enlargement to be significantly correlated with neuropsychological deficit. Using three rules, based on their results and results from previous LNBB studies, Golden and associates were able to correctly classify 90% of their subjects with respect to CT evidence of ventricular enlargement. In a follow-up investigation Golden, Graber et al. (1980) applied the same rules to an independent, random sample of schizophrenic patients and obtained a hit rate of 81% in identifying the presence/absence of ventricular enlargement and a 90% hit rate in identifying sulcal enlargement. In a third study, Golden, MacInnes et al. (1982) used their criteria to correctly classify 77% of 43 unselected schizophrenics on the basis of normal/abnormal CT findings. Based on this series of investigations, it was concluded that impairment on 5 or more of the 14 scales were generally associated with CT abnormalities, and that eight or more impaired scores plus the pathognomonic scale was almost invariably

associated with structural CT changes.

While the investigations carried out by Golden and co-workers suggest that LNNB scores can discriminate with considerable accuracy schizophrenics with and without CT abnormalities, there are problems with these studies that limit their interpretation. Zec and Weinberger (1986) claim that the most serious of these problems is measurement error in calculating VBRs; that the third ventricle was perhaps mistakenly measured in addition to the lateral ventricles. If that was true then the technique used for measuring VBRs would overestimate the percentage of abnormal VBRs, perhaps by as much as 40%, resulting in a spuriously high hit rate. On the basis of purported VBR measurement problems, Zec and Weinberger (1986) conclude that the concept of classification of normal and abnormal CT on the basis of LNNB results is of questionable validity.

The HRB has also been used to explore the relationship between neuropsychological performance and CT findings. Donnelly et al. (1980) obtained neuropsychological and CT data on 35 chronic schizophrenic patients in a attempt to identify blindly those schizophrenic patients with positive and negative CT scans on the basis of degree of neuropsychological impairment. Using a composite index of cerebral impairment (Average Impairment Index) Donnelly and associates were able to

predict ventricular enlargement with 80% accuracy. Citing two unpublished CT-HRB studies with large samples (n=60), Zec and Weinberger (1986) noted that performance on the HRB, using the Halstead Impairment Index as a cutting score, accurately classified 67% into CT normal and abnormal categories. Interestingly, 85% of the misclassifications were cases in which neuropsychological performance was impaired but CT findings were negative. In these cases, the suggestion was made that an organic basis should still be considered because the relationship between CT abnormalities and organic impairment is not a perfect one. For example, an appreciable number of cases of dementia have been reported without evidence of atrophy. Therefore there is no reason to suspect that a strong relationship between cognitive impairment and CT abnormalities necessarily exists. In fact, neuropsychological measures may be more sensitive to organic impairment than CT which detects only gross structural lesions.

In a more recent investigation, Pandurangi et al. (1986) reported greater neuropsychological impairment on two of three commonly used HRB general impairment indices in a small (n=6) group of chronic schizophrenics with enlarged ventricles as compared to a slightly larger (n=11) group without CT abnormality. Areas of hyperdensity were also noted in the enlarged ventricle group. The percentage

of patients falling in the impaired range on the Halstead Impairment Index, the Per Cent Impaired Ratio and, the Average Impairment Index were 100, 83 and 67% respectively. Boucher et al. (1986) employing the same three indices of neuropsychological impairment in a young chronic schizophrenic population (n=20) also found the easier-to-obtain Halstead Impairment Index (88% hit rate) to be at least as good as, and possibly better than the other two indices in separating CT normal from CT abnormal patients. These studies indicate that the HRB and HRB impairment indices are helpful in separating those subgroups of schizophrenics with CT abnormality from those without.

The only CT study using both the HRB and the LNNB to study the relationship between ventricular size and neuropsychological functioning was carried out by Carr and Wedding (1984). In their sample of chronic schizophrenic outpatients (n=21) no significant relationship was found between VBRs and neuropsychological test scores. This negative result was taken to reflect the possibility that patients with large ventricles were underrepresented in the study.

The results of CT-HRB and CT-LNNB studies generally suggest a significant relationship between CT abnormality (usually ventricular enlargement as assessed by VBR) and neuropsychological status, although negative findings have

been reported (e.g., Obiols et al., 1987). Despite methodological limitations, small sample sizes and discrepancies between patient sample characteristics, the preponderance of evidence would seen to suggest a positive relationship between neuropsychological impairment and CT abnormalities. This relationship appears strongest when the Halstead Impairment Index and VBRs are used as dependent variables in a chronic schizophrenic population. One limitation of these studies, however, is the failure to evaluate in many studies CT abnormalities other than ventricular enlargement and sulcal widening. CT studies in schizophrenia have suggested density changes, cerebellar atrophy and unusual asymmetries which, if found, would obscure the association between neuropsychological performance and the CT abnormality being studied. Despite these limitations the general conclusion can be drawn that a substantial proportion of schizophrenics show evidence of significant neuropsychological dysfunction and this dysfunction is typically associated with structural brain changes.

Another question in assessing brain dysfunction in schizophrenia using neuropsychological tests is whether impaired performance on clusters of tests known to be selectively sensitive to localized cortical lesions provides any basis for inferences regarding cerebral dysfunction. Here evidence for localized cerebral

dysfunction in schizophrenia will be presented.

The search for the "schizophrenic lesion" has been described as "a journey throughout the central nervous system" (Goldstein, 1986). Numerous studies (e.g., Kolb & Whishaw, 1983) have examined various anterior versus posterior, right versus left, and cephalo versus caudal hypotheses with limited success. The beginning of this interest is generally attributed to Flor-Henry (1969) who noted resemblances between schizophrenic behavior and the behavior of individuals with temporal lobe epilepsy. These early observations ultimately led to the hypothesis that schizophrenia is associated with a "yet to be delineated deficit involving the left cerebral hemisphere" (Golden, 1986). Others, as indicated, have advocated the frontal lobes as the locus of the schizophrenic lesion. Kolb and Wishaw (1983) found schizophrenic patients significantly impaired on tests sensitive to left or right frontal or temporal lobe lesions and on that basis concluded that schizophrenia results, in part, from bilateral dysfunction of the frontal and temporal lobes. Taylor and Abrams (1984) also reported bilateral impairment that was comparatively worse in dominant frontotemporal regions in their sample of 62 schizophrenics. Following a major review of the neuropsychological literature, Seidman (1983) concluded that, when found, neuropsychological impairment tends to be mild to moderate in severity and more likely to

be diffuse or bilateral than focal. The picture of global intellectual impairment has been used as support for a return to the idea of dementia praecox in some schizophrenics. Similar conclusions have been drawn on the basis of neuropathological findings as well (Stevens, 1983).

Longitudinal studies of cognitive functioning in schizophrenia suggest, however, that most do not become demented if one defines dementia as a progressive deterioration of intellectual functions (Goldstein, 1986). Several reports (Schwartzman, 1962; Smith, 1964) have indicated that the intellectual deficit in schizophrenia occurs during onset of the disease and that no further impairment can be identified subsequent to that period other than the effects of normal aging which are also seen in normal populations (Klonoff et al., 1970). Thus it has been concluded (Goldstein, 1986) that, although intellectual deterioration during the onset of schizophrenia has led some to conceptualize the disorder as a progressive dementia, long term observation of schizophrenic patients suggest that most do not become demented at all, but remain the same, or sometimes show evidence of improvement. Thus neuropsychological studies have contributed to the notion that schizophrenia is the result of a more or less static process (Seidman, 1983; Goldstein, 1986) characterized by episodes of acute

exacerbations of illness intermixed with more quiescent periods.

The recent association of negative symptoms (e.g., Silverstein & Arzt, 1985) with cortical atrophy and neuropsychological impairment has led several authors to speculate that these manifestations may provide a basis for a theoretically and neurologically coherent subgroup of schizophrenia. In terms of psychopathology, negative symptoms are the signs of deficit in the cognitive or affective sphere, such as blunted affect or intellectual impairment, whereas positive symptoms include hallucinations and delusions. During the acute phase of illness, positive symptoms are usually more pronounced and in remission, the schizophrenic may be emotionally flat and withdrawn. While neuropsychological tests do not evaluate, nor do they attempt to systematically elicit such positive symptoms as hallucinations and delusions, they do assess many of the negative ones, particularly in the cognitive and perceptual domain (Goldstein, 1986). In subsequent sections the relative contribution of neuropsychology to the assessment and management of both positive and negative symptoms will be explored.

Summary

In the preceding sections data supporting the notion of schizophrenia as a brain disease have been

presented. Converging data from neurological, neurodiagnostic and neuropsychological investigations all suggest that intrinsic brain factors are intimately involved in the schizophrenic process. In an extensive review of the literature concerning brain disease in schizophrenia, Seidman (1983) concluded that the data as a whole more strongly support the presence of bilateral rather than unilateral brain dysfunction. The data presented here, encorporating the results of more recent investigations, including preliminary findings from new technologies (e.g., MRI), continue to support that general hypothesis. However, it is interesting to note that the majority of positive findings with respect to abnormal structure and functional asymmetries, when found, implicate more frequently left rather than right and anterior rather than posterior cortical areas. Furthermore, the observation that schizophrenics with sulcal enlargement tend not to have enlarged ventricles and vice versa suggests that there may be at least two different types of pathological processes occurring in schizophrenia. For example, ventricular enlargement may reflect atrophy of deep brain (i.e., subcortical) structures, while sulcal enlargement may reflect diffuse cortical atrophy. The repeated lack of association between indices of ventricular enlargement and sulcal enlargement has fueled recent speculation about two different subgroups of schizophrenia

with independent etiological factors and clinical manifestations (Crow, 1980; Andreasen, 1982; Dewan et al., 1986).

STUDY I
NEUROPSYCHOLOGICAL CHARACTERISTICS OF POSITIVE VERSUS NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Traditionally speaking, North American psychiatry has always emphasized the importance of subtyping. Consequently, the history of the nosology of schizophrenia has also been influenced by the search for meaningful subtypes. Over the years such cross-sectional subdivisions as schizoaffective versus non-affective and paranoid versus non-paranoid as well as other sets of subtypes emphasizing longitudinal course such as acute versus chronic, process versus reactive, and good versus poor prognosis have all been explored. Many of these classification systems have now been dismissed because they yield no clinically significant aetiological, treatment or prognostic information (Andreasen, 1982). Surprisingly, until recently few classification systems have been made which relate to either functional brain systems or areas of brain dysfunction.

The Positive/Negative Symptom Distinction

The search for relatively discrete subtypes of schizophrenia has led to a distinction based on whether the symptoms of the disorder are predominantly positive (or

florid) or whether they are predominantly negative (or defect). Much of the recent appeal of this distinction lies in the fact that it unites our current understanding of phenomenology, pharmacology, pathophysiology and neurocognitive features into a single comprehensive hypothesis (Andreasen, 1985a) based on the theory that positive and negative symptoms of schizophrenia form the basis for two distinct subtypes. This distinction has now gained prominence in schizophrenia research (Bilder, Mukherjee, Reider & Pandurangi, 1985), and while the origin of this concept in neurology can be argued (Berrios, 1985), there is little doubt about its impact on current research (Lewine, 1985).

Much of the impetus for recent empirical work, which has resulted in the revitalization of the positive-negative symptoms distinction, can be attributed to Crow (1980) and Andreasen (1982; Andreasen & Olsen, 1982).

Crow (1980) proposed that "two syndromes of schizophrenia can be distinguished in those diseases currently described as schizophrenic." (p. 68). The first (the Type I syndrome, equivalent to "acute schizophrenia," and characterized by the positive symptoms - delusions, hallucinations, and thought disorder) was felt to be in some way associated with a change in dopaminergic transmission, while the second (the Type II syndrome,

equivalent to the "defect state" and characterized by negative symptoms - affective flattening and poverty of speech) was thought to be unrelated to dopaminergic transmission but associated with intellectual impairment and structural brain changes. Crow (1980), in a review of the literature on schizophrenia, was among the first to propose that two syndromes can be distinguished among those diseases currently described as schizophrenic and that each may be associated with a specific pathological process. In general, the Type I syndrome is characterized predominantly by symptoms which are not part of the normal behavioral repetiore but emerge in the face of illness, whereas the Type II syndrome tends to be characterized by a diminished capacity to engage in certain behaviors resulting in impoverished thought or action. Crow (1980) went on to postulate that Type I symptoms are reversible whereas Type II symptoms are more or less irreversible. Also, when the clinical picture was predominated by Type I symptoms a potential response to neuroleptics was predicted. In the case of predominantly Type II symptoms, the prognosis for long-term adjustment was described as "poor". Crow also observed that in some cases episodes of Type I symptoms (equivalent to "acute schizophrenia") may be followed by the development of a Type II syndrome, or that both may be present together. Nevertheless, when Type II symptoms were present, either alone or in combination with Type I

symptoms, the prognosis was generally "graver". However, because positive and negative symptoms are not well defined, the diagnosis of a Type I or Type II syndrome is sometimes difficult to establish (Crow, 1980).

The positive/negative symptom distinction has also been extensively examined by Andreasen (1982, 1985a; Andreasen & Olsen, 1982) in the form of a hypothesis for identifying discrete subtypes of disease within the schizophrenic realm. Like Crow (1980), Andreasen hypothesized that patients with prominent positive symptoms (delusions, hallucinations, positive formal thought disorder, or bizarre behavior) are likely to differ in a variety of important ways from patients who have prominent negative symptoms (alogia, affective blunting, avolition, anhedonia-asociality, and attentional impairment). Her hypothesis was based on the position that negative symptoms seem to define one end of a continuum of disorders which appear to be correlated with poor premorbid adjustment, better response to neuroleptic therapy, a chronic course and poor outcome, cognitive impairment, and a different underlying pathologic process such as atrophic changes in the brain. On the other hand, positive symptoms seemed likely to be correlated with better premorbid adjustment, better response to neuroleptic therapy, a less malignant course, a normal sensorium, and an underlying pathologic process that may be predominantly neurochemical (Andreasen,

1982).

Andreasen (1982) examined such variables as premorbid adjustment (based on Phillips Scale; Harris, 1975), previous course of illness, previous treatment and cognitive dysfunction in a sample of 52 patients who met DSM III criteria for schizophrenia. Using the criteria found in Table 1, Andreasen found that 16 met criteria for negative schizophrenia, 18 for mixed schizophrenia and 18 for positive schizophrenia. Computerized tomographic (CT) scans of the brain were also obtained and ventricular-brain ratios (VBRs) calculated.

Table 1

ANDREASEN'S (1982) CRITERIA FOR SUBTYPING SCHIZOPHRENIA

POSITIVE SCHIZOPHRENIA

1. At least one of the following is a prominent part of the illness:
   (a) Severe hallucinations that dominate the clinical picture (auditory, haptic, or olfactory) (The judgement of severity should be based on various factors such as persistence, frequency, and effect on lifestyle.).
   (b) Severe delusions (may be persecutory, jealous, somatic, religious, grandiose, or fantastic) (The judgement of frequency should be made as described for severity.).
   (c) Marked positive formal thought disorder (manifested by marked incoherence, derailment, tangentiality, or illogicality).
   (d) Repeated instances of bizarre or disorganized behavior.
2. None of the following is present to a marked degree:
   (a) Alogia
   (b) Affective flattening
   (c) Avolition-apathy
   (d) Anhedonia-asociality
   (e) Attentional Impairment

Table 1 (con't)
NEGATIVE SCHIZOPHRENIA

1. At least two of the following are present to a marked degree:
   (a) Alogia (e.g., Marked poverty of speech, poverty of content of speech).
   (b) Affective Flattening (e.g., Inability to feel and express emotion).
   (c) Anhedonia-asociality (e.g., Inability to experience pleasure or to feel intimacy, few social contacts).
   (d) Avolition-apathy (e.g., inability to follow through on tasks, anergia, impersistence at work or school).
   (e) Attentional Impairment.
2. None of the following dominates the clinical picture or is present to a marked degree:
   (a) Hallucinations
   (b) Delusions
   (c) Positive Formal Thought Disorder
   (d) Bizzare Behavior

MIXED SCHIZOPHRENIA

This category includes those that do not meet criteria for either positive or negative schizophrenia, or meet criteria for both (Andreasen & Olsen, 1982, p. 790).

Cognitive function was assessed using the Mini Mental Status Exam. The Global Assessment Scale (GAS) was used as an overall index of the severity of illness at the time of evaluation. As hypothesized, the three patient groups differed significantly on all variables. The schizophrenics with negative symptoms had significantly larger VBRs than did patients with mixed or positive schizophrenia. Based on these findings, Andreasen suggested that negative symptoms may have, as an underlying pathology, a process involving cortical atrophy. Andreasen (1982) also observed that negative schizophrenics obtained significantly lower scores on the Mini Mental Status Exam,

reflecting greater intellectual impairment, and lower GAS ratings on admission than did the patients with positive symptoms, indicating poorer premorbid adjustment. Generally, Andreasen (1982) interpreted her findings as providing support for the subtyping of schizophrenia according to the presence/absence of positive and/or negative symptoms.

One limitation of Andreasen's 1982 study is that her data are cross-sectional. Longitudinal study is clearly needed to explore the evolution of positive and negative symptoms over time in order to address issues of reversibility and stability. Clinical observation (e.g., Snezhnevsky, 1968) has suggested that patient's whose symptoms are initially negative tend to remain negative when followed longitudinally, whereas patients with initial positive symptoms may eventually develop negative symptoms. However, until recently there was little empirical evidence to support this clinical lore.

In a recent investigation of the relative stability of positive and negative symptoms, Johnstone, Owens, Frith and Crow (1986) followed 92 chronic schizophrenics over a 4 year period. Based on data from serial assessments the study provides preliminary support for the general view that negative symptoms (i.e., behavioral deficits) are relatively stable, whereas positive symptoms (i.e., behavioral excesses) are relatively variable and show the

greater response to drugs. It was noted, however, that negative features were not entirely irreversible but in some instances either resolved or were alleviated.

Following this renewed interest in the phenomenology of positive and negative schizophrenia, Andreasen (1982; 1983) introduced an instrument for assessing particularly negative symptoms, since most positive symptoms were already well defined and perhaps overly represented in currently available research instruments such as the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer, 1978) and the DSM III. This new instrument, called the Scale for the Assessment of Negative Symptoms (SANS) contains items for rating 30 purportedly negative symptoms listed under 5 major symptom complexes (alogia, 6 items; affective flattening or blunting, 9 items; avolition-apathy, 5 items; anhedonia-asociality, 6 items; and attentional impairment, 6 items) called "global symptoms". The global symptoms were described as "empirically derived" although the description of their origin suggests that clinical experience was a contributing factor.

Each of the five global measures from the SANS is broken down into observable behavioral components which are then rated on a six-point scale. Patient interviews and observations of behavior provide the information necessary for making each rating. Data can also be obtained from

other sources if it will assist in the rating process. The instrument was developed with the expectation that the appropriate "time set" for rating symptoms would include the net behavior witnessed over the past month.

The SANS provides several different types of scores. A global rating for each of the five symptom complexes serves as an index of the severity of each symptom. The sum of these Global Ratings (Summary Score) may be used to assess the severity of the negative symptom syndrome as a whole. In addition, a Composite Score may be obtained by summing the ratings of all 30 individual items as an alternative index of the severity of the negative symptom picture.

The reliability of the SANS has also been assessed (Andreasen, 1982) using an interrater reliability design. Two Masters-level research assistants interviewed 26 patients and made ratings on the basis of behavior, medical records, staff input and self-report. The interrater reliability of negative symptoms was consistently high across individual items (.70-.93) and subscale scores (.86-.92), as well as for the Summary Score (.84) and Composite Index (.92). In all cases inter-rater reliability was judged sufficiently high to defend its use in research.

In summary, it has been proposed that dividing schizophrenic patients according to positive and negative

symptoms may provide a useful subtyping schema (Andreasen, 1982) and that two distinct syndromes in schizophrenia can be discerned on the basis of phenomenological data. Citing abundant evidence of structural and functional brain abnormalities in at least some subtypes of schizophrenia, Crow (1980) hypothesized that negative symptoms are associated with structural abnormalities (e.g., ventricular enlargement), as evidenced on CT, whereas positive symptoms are not. Positive symptoms, on the other hand, are purportedly related to biochemical (e.g., dopaminergic) rather than structural brain changes. The latter hypothesis being supported by data which suggest positive symptoms respond better to neuroleptics than do negative ones (e.g., Johnstone et al., 1978) and, that amphetamines exacerbate the condition of patients with positive but not negative symptoms (e.g., Angrist et al., 1980). In addition, positive symptoms are said to be relatively variable whereas negative symptoms are relatively fixed (Sneznevsky, 1968), implying a more chronic course (Crow, 1980)

Another assumption of the two-syndrome hypothesis is that negative symptoms are uniquely associated with generalized cognitive impairment, however evidence for this purported relationship is largely indirect. For example, inasmuch as negative symptoms are associated with ventricular enlargement (Andreasen, 1982), and ventricular

enlargement in turn with neuropsychological impairment (e.g., Golden et al., 1980), some evidence is available. Other indirect evidence comes from neuropsychological studies which report gross cognitive impairment in chronic schizophrenics (e.g., Klonoff et al., 1970). Again, inasmuch as chronic schizophrenia is associated with predominantly negative symptoms (Crow, 1980), then indirect evidence of cognitive impairment as a characteristic of negative-symptom schizophrenia is also available. However, despite its theoretical significance, the hypothesis that negative symptoms are uniquely associated with generalized cognitive impairment has received little attention from researchers (Green & Walker, 1985; 1986a; 1986b).

Preliminary investigations now suggest that while the two-syndrome hypothesis of schizophrenia has become immensely popular, the symptom picture may not be so dichotomous as it is sometimes presented. For example, Andreasen and Olsen (1982) found that a significant proportion of general schizophrenics (as much as 35%) do not demonstrate predominantly positive or negative symptoms. Furthermore, assumptions about the relative stability, neuroleptic responsivity and neuropsychological characteristics of positive and negative symptoms are now being re-examined (Green & Walker, 1985; 1986a, 1986b; Johnstone et al., 1986; Liddle, 1987; Volkow et al., 1987), calling for a redefinition of the concept. Discrepancies

between early postulates (Crow, 1980; Andreasen, 1982) and recent empirical data (e.g., Johnstone et al., 1986) regarding differences in symptom stability and neuroleptic responsivity will be presented later. Presently, attention is focused on neuropsychological data which fail to support the presumed association between cognitive dysfunction and negative symptoms.

Green and Walker (1985) examined neuropsychological performance in relation to symptomatology in a group of 44 schizophrenics, 15 bipolar patients and 12 normal control subjects. For purposes of data analyses, schizophrenic patients were divided into three groups (positive, negative and mixed). The central finding of the Green and Walker study was that positive and negative symptoms were associated with different patterns of performance deficit on neuropsychological tests. Negative symptoms were associated with poorer performance on tests that measure visuo-motor and visual-spatial skills, whereas positive symptoms were related to deficits on tests that involve short-term verbal memory. These data stand in contrast to the notion that cognitive deficits are uniquely associated with negative symptoms. Instead, the results suggest that there may be specific cognitive correlates of both positive and negative symptoms (Green & Walker, 1985). Group comparisons were consistent with earlier findings of generalized deficits in schizophrenia.

Green and Walker (1986), in a subsequent investigation, also reexamined the assumption that attentional impairment is one of the global symptoms of negative schizophrenia. While impaired attention has long been considered a core symptom of schizophrenia, attentional impairment is included as a subscale only on the SANS. Green and Walker, again subdivided their schizophrenics (n=41) into the same trichotomous grouping. All subjects were administered a dichotic listening and digit-span task as measures of attention. The digit-span tasks consisted of two conditions; distraction and nondistraction. In the former condition, subjects were instructed to attend to target stimuli (presented in a female voice) and to ignore distractor stimuli read by a male during the interval between target digits. In general, the results of this study were inconsistent with the assumption that deficits in attention are uniquely associated with negative symptoms. In fact, negative symptom schizophrenics showed significant performance deficits on either task relative to controls. In contrast, positive symptom schizophrenics performed worse than normals on both conditions of the digit-span task with greater impairment in the distraction condition. The results were interpreted as evidence for a deficit in selective attention in positive schizophrenia. In an earlier study, Green and Walker (1984) found that negative

symptom schizophrenics were deficient in sustained attention based on their performance on a backward masking task. Taken together, these latter studies suggest that global attentional impairment is not a correlate of negative symptom schizophrenia but there may be different patterns of attentional deficits associated with the two types of symptoms.

In conclusion, the positive/negative symptom approach to subtyping in schizophrenia has recently aroused considerable interest, primarily because it integrates disparate observations into a unitary theory. In addition, the classification of schizophrenic symptoms along positive/negative dimensions appears to have at least some prognostic significance, however, the positive versus negative symptom distinction requires further study. Of special interest are the cognitive/attentional correlates of positive and negative symptoms in schizophrenia, an area which has received little research attention. While it is generally held that negative symptoms are uniquely associated with cognitive and attentional impairment (Crow, 1980; Andreason & Olsen, 1982), recent neuropsychological studies (Bilder et al., 1985; Green & Walker, 1985; 1986a, 1986b; Walker & Harvey, 1986) suggest that each syndrome may be associated with a unique pattern of deficit.

CONCLUSIONS

In conclusion, there is now abundant evidence, from diverse neurodiagnostic techniques and neuropsychological studies, that a significant proportion of schizophrenics show evidence of brain disease (Henn & Nashrallah, 1982) and attendant neuropsychological deficits (Goldstein, 1986). Studies generally seem to implicate both cortical and subcortical structures, taken as evidence for diffuse involvement of multiple brain functions (Seidman, 1983). With this understanding that the disease has a clear organic basis a neuropsychiatry (Goldstein, 1986; Cleghorn, 1988) as well as neuropsychology of schizophrenia has now been firmly established as a legitimate area of research.

Clinical and neurodiagnostic evidence indicate that the symptomatology of schizophrenia reflect, in part, the behavioral consequences of both structural and biochemical changes in the brain (Andreasen, 1984b). Support for a neurochemical disturbance stems from the observation that delusions and hallucinations often remit following administration of neuroleptic drugs (Johnstone et al., 1978) and the fact that all established neuroleptic drugs have dopamine (DA) agonist potency (Julian, 1978). The "dopamine hypothesis of schizophrenia" (see McKenna, 1987), a biochemical theory, holds that hallucinations and delusions (both positive symptoms) are the result of a

pathologic increase in DA transmission at the level of the post-synaptic receptor, possibly specific to the D-2 DA receptor (Crow, Ferrier & Johnstone, 1986). On the other hand, various brain-imaging techniques have revealed, repeatedly, various gross structural abnormalities, most notably ventricular enlargement, in a significant proportion of schizophrenics (Weinberger et al., 1979a), and more recent technologically advanced MRI studies continue to support this hypothesis (e.g., Rossi et al., 1989; Suddath et al., 1989). Thus it has been proposed that a single dimensional view of the neuropathology of schizophrenia is no longer tenable and that it is necessary to adopt, at least, a two-syndrome concept (Crow, 1980; Andreasen, 1982, 1985a; Andreasen & Olsen, 1982).

Crow (1980) and Andreasen and Olsen (1982) have suggested that schizophrenic symptoms can be classified as either positive (as in the case of florid symptoms) or negative (as in the case of defect states). These researchers postulate that positive and negative symptoms reflect different neuropathological substrates. According to their model, positive symptoms reflect a biochemical lesion whereas negative symptoms reflect a structural lesion (Crow, 1980; Andreasen & Olsen, 1982).

The positive versus negative symptom distinction has proven to have at least some validity in defining subtypes within the schizophrenic realm, not only with

respect to defining different underlying pathologies but also with separate neuropsychological characteristics, treatment implications and prognoses (Crow, 1980; Andreasen, 1982). According to Crow's (1980) typography for example negative symptoms (e.g., flat affect, poverty of speech and expressive gesture, psychomotor slowing, anhedonia, and attentional deficits) are characteristics of a subtype of schizophrenia characterized by a chronic course of illness, poor response to neuroleptics and cognitive deficits. Alternatively, positive symptoms (e.g., hallucinations, delusions, bizarre behavior and thought disorder) are considered characteristic of another subtype more often associated with acute illness, a favorable response to neuroleptic medication and relatively intact cognitive functions (Crow, 1980, Crow et al., 1982).

While the two-syndrome hypothesis of schizophrenia is attractive because it integrates sometimes seemingly disparate findings into a unitary theoretical model with practical treatment and prognostic implications, many of its assumptions have not been subject to empirical scrutiny. In fact, many of the assumptions have received relatively little attention from researchers. The purpose of this investigation is therefore to examine the various assumptions of Crow (1980) and Andreasen and Olsen (1982) regarding the neuropsychological characteristics of patients exhibiting positive versus negative symptoms of

schizophrenia.

AIM:

The purpose of this study is, generally, to examine the neuropsychological characteristics of positive- and negative symptom schizophrenics based on Andreasen and Olsen's (1982) definition of the symptom complexes (see Table 1, p. 62). In particular, the cognitive and attentional correlates of positive versus negative symptoms of schizophrenia will be examined on the basis of global performance comparisons as well as deficit pattern analyses. Furthermore, in recognition of the fact that the subtyping schema does not wholly divide all schizophrenics into two discrete syndromes, the neuropsychological characteristics of schizophrenics whose symptom picture is mixed (reflecting, presumably, co-existing dimensions of neuropathology) will also be explored.

Hypothesis 1

According to the two-syndrome hypothesis of Crow (1980) and Andreasen (1982) neuropsychological impairment is, purportedly, characteristic of negative- but not positive-symptom schizophrenia. Most of the support for this assumption is, however, largely intuitive rather than empirically derived. Furthermore, what empirical evidence

exists is largely indirect. For example, some studies show that neuropsychological impairment is associated with ventricular enlargement (e.g., Golden et al., 1980) and ventricular enlargement with negative symptoms (e.g., Johnstone et al., 1976), however, few studies have examined the relationship between neuropsychological functioning and negative (or positive) symptoms directly.

Preliminary neuropsychological data (Bilder et al., 1985; Green & Walker, 1985, Kaplan et al., 1988) generally fail to support the assumption (Crow, 1980; Andreasen & Olsen, 1982) that negative symptoms are uniquely associated with cognitive impairment. For example, Green and Walker (1985) examined patterns of deficit in 44 schizophrenics and identified specific cognitive correlates of both positive and negative symptom dimensions. While these studies suggest that specific (qualitative) deficits patterns may be associated with various symptom complexes they fail to address the more general question of whether or not negative-symptom schizophrenics show more overall cognitive impairment than positive-symptom schizophrenics. Thus, the hypothesis that negative-symptom schizophrenics are either uniquely or quantitatively more impaired than positive-symptom schizophrenics will be tested here.

In order to test this hypothesis, positive- and negative-symptom schizophrenics will be compared on the basis of several global indices of neuropsychological

impairment (e.g., Halstead Impairment Index; Reitan & Wolfson, 1985). The finding that negative-symptom schizophrenics are significantly impaired on any or all of the global impairment indices relative to other subtypes would provide varying degrees of support for the assumption (Crow, 1980; Andreasen & Olsen, 1982) that negative but not positive symptoms are associated with cognitive impairment. Alternatively, failure to find such differences would suggest that cognitive impairment may not be a unique or defining characteristic of the negative symptom syndrome as portrayed in the literature.

Hypothesis 2

Recent neuropsychological studies (Bilder et al., 1985; Green & Walker, 1985; Kaplan, 1988) suggest not only that cognitive impairment may not be specific to negative-symptom schizophrenia, but that positive and negative symptoms may each be associated with a unique pattern of cognitive deficits. Green and Walker (1985) in particular found that negative symptoms were associated with poorer performance on tests that measure visual-spatial and visuo-motor skills, while positive symptoms were related to deficits on tests that involve short-term verbal memory. These findings were also at least partially replicated by Kaplan et al. (1988) who reported, in part, less adequate verbal recall among

positive- versus negative-symptom schizophrenics.

The general finding that negative symptoms appear associated with deficits on non-verbal, visual-spatial tasks and positive symptoms with deficits on verbally-mediated tasks raises the question of a possible lateralizing significance to these (Green & Walker, 1985; Kaplan et al., 1988) findings. Specifically, the data of Green and Walker (1985) may be interpreted as support for the hypothesis that positive symptoms are associated with underlying left hemisphere dysfunction and negative symptoms with underlying right hemisphere dysfunction. Goldstein (1986) has also speculated that "patients with left hemisphere deficiencies may be primarily Type I" (p. 164) (positive-symptom) schizophrenics.

While the possibility of lateralized cognitive dysfunction is raised, or at least implied, by both Green and Walker (1985) and Goldstein (1986), the association between positive versus negative symptoms and right versus left hemisphere dysfunction has not been examined directly.

The second hypothesis, therefore, concerns the question of whether qualitative differences in pattern of neuropsychological deficit, if found, are of lateralizing significance. In the present study this hypothesis is examined by employing a laterality index (Reitan, 1986) of right-left differences in neuropsychological performance in relation to positive versus negative symptoms of

schizophrenia. A significant relationship between negative symptoms and right hemisphere dysfunction and/or positive symptoms and left hemisphere dysfunction would pose interesting theoretical questions regarding the neurological substrata of various psychiatric symptoms.

Hypothesis 3

The third hypothesis concerns the assumption (Andreasen, 1982; Andreasen & Olsen, 1982) that attentional deficits are a unique characteristic of negative-symptom schizophrenia, thereby justifying the inclusion of an Attention subscale on the Scale for Assessment of Negative Symptoms in Schizophrenia (SANS; Andreasen, 1982). In a series of investigations Walker and associates (Green & Walker, 1986a, 1986b; Walker & Harvey, 1986) specifically examined attentional performance correlates of positive versus negative symptoms of schizophrenia and have failed, repeatedly, to find support for Andreasen's (1982) position that attentional impairment is a unique characteristic of negative-symptom schizophrenia. Rather, Green and Walker (1986a, 1986b) suggest specific attentional deficits related to both positive and negative symptom dimensions. Specifically, positive-symptom schizophrenics appear to exhibit deficits in selective attention whereas negative-symptom schizophrenics showed greater vulnerability to "backward masking" (interpreted as

evidence for a perceptual organization deficit and a concomitant processing slowdown).

In the present study, the hypothesis that attentional deficits are uniquely associated with negative-symptoms will be tested by examining performance across subtypes on several neuropsychological tests tapping various dimensions of attention (i.e., selective versus sustained, auditory versus visual) and concentration. A failure to find group differences would stand in contrast to the position that attentional deficits are unique to negative-symptom schizophrenia (Andreasen & Olsen, 1982) and will possibly detract from the validity of the SANS Attention subscale as a global index of negative-symptom schizophrenia. The content validity of the SANS Attention subscale will also be challenged by examining the correlations between attention ratings obtained from psychiatric interview and objective neuropsychological test findings.

Hypothesis 4

The fourth hypothesis concerns the general relationship between psychiatric symptoms and neuropsychological functioning. While it has been proposed that the positive versus negative symptom distinction is an useful typography in that it unites phenomenological, pharmacological and cognitive features into a single

comprehensive hypothesis (Andreasen & Olsen, 1982) the model has been criticized as an oversimplification of what would otherwise appear to be a complex set of relationships (Andreasen, 1985a). With respect to cognitive features there is little empirical evidence to support the hypothesis that the positive versus negative symptom distinction is useful for predicting neuropsychological functioning in schizophrenia.

Existing studies (e.g., Green & Walker, 1985; Kaplan et al., 1988) appear to suggest that the relationship between positive versus negative symptoms and neuropsychological functioning is insufficient to allow for meaningful prediction of cognitive deficit. The data of Green and Walker (1985), for example, provide only partial support for the validity of the positive versus negative distinction inasmuch as distinct neuropsychological deficits may be associated with each symptom complex. However, overall performance or specific performance patterns were not strongly linked to either schizophrenic subtype. Alternatively, Bilder et al. (1985) has proposed that symptom profiles independent of the positive versus negative distinction may be more valid predictors of neuropsychological impairment.

Lastly, the present study examines the hypothesis that other symptoms, or combination of symptoms, may be more useful than the positive versus negative distinction

in predicting the presence or absence of neuropsychological impairment among schizophrenics. In order to test this hypothesis, regression analysis, using individual symptom ratings as predictor variables and a neuropsychological impairment index as the dependent variable, will be employed.

In summary, the present study was designed to test the following specific hypotheses:

1. Negative symptom-schizophrenics are either uniquely or quantitatively more impaired on neuropsychological tests than positive-symptom schizophrenics.

2. Negative symptoms are associated with impairment on neuropsychological tests that are sensitive to right hemisphere dysfunction and positive symptoms with impairment on tests that are sensitive to left hemisphere dysfunction.

3. Impaired attention is a unique and therefore defining characteristic of negative-symptom schizophrenia.

4. Other symptom combinations independent of the positive versus negative symptom distinction allow for more accurate prediction of neuropsychological functioning in schizophrenia.

In examining these hypotheses this study addresses the following general questions: 1) Is the positive-negative symptoms distinction useful for predicting the degree and/or extent of neuropsychological impairment in schizophrenia? 2) Are qualitative differences in pattern of neuropsychological deficit between positive and negative symptom schizophrenics, if found, of lateralizing significance? 3) Are attentional deficits a defining characteristic of the negative symptom

complex as defined by Andreasen and Olsen (1982) or do qualitative differences exist between subtypes as suggested by Green and Walker (1986a, 1986b)? 4) Is there any particular symptom, or combination of symptoms which, when present (or absent), seem to be associated with neuropsychological impairment among schizophrenics, independent of the positive versus negative symptom distinction?

METHOD

Subjects:

The study was conducted with the co-operation of the Departments of Psychology and Psychiatry (Community Psychiatry Services, East Region Mental Health Services), St. Joseph's Hospital, Hamilton, Ontario. Subjects for this study were 40 chronic schizophrenic patients obtained from two regionally-based outpatient psychiatric clinics. The two clinics do not differ from each other in any significant way other than serving separate catchment areas within the City of Hamilton. Since the catchment areas likely differ in the socio-economic status of their residents, an attempt was made to ensure that patients from both regions were fairly equally represented.

All registered psychiatric patients at these clinics who met Diagnostic and Statistical Manual of Mental Disorders (DSM-III; American Psychiatric Association, 1980) criteria for schizophrenia were considered potential subjects for the study. DSM-III diagnoses were based on chart information. (McGlashan (1984) has demonstrated that DSM-III diagnoses can be quite readily obtained using only medical records). Exclusion criteria were a history of prolonged alcohol and/or drug abuse, known neurological

disease (e.g., epilepsy), mental retardation, and schizoaffective disorder.

Schizophrenic patients who met inclusion/exclusion criteria were invited to participate. Sample size was calculated based on the retest reliability of the Category Test (Matarazzo, Mattarazzo, Weins, Gallo & Klonoff, 1976) in schizophrenic subjects and a .90 probability of Type II error at the .05 significance level. The 40 recruited subjects each signified, in writing, their informed consent (see Appendix A) prior to participating in the assessment procedures. All subjects attended a structured psychiatric interview, underwent a battery of neuropsychological tests (see Appendix B) and completed a self-report questionnaire. One subject refused to complete the neuropsychological battery. They received no remuneration for their participation. The study was conducted between May, 1986 and August, 1987.

Assessment Procedures:

i. Psychiatric Interview

All volunteers attended a structured psychiatric interview during which the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983) and the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984a) were administered. The interviews took on average 1- 1.5 hours to conduct. SANS and SAPS scores were used,

variously, as the basis for subtyping.

Scale for Assessment of Negative Symptoms

The SANS consists of 20 items and 5 global ratings designed to assess the extent to which the subject manifests the following negative symptoms of schizophrenia: affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality, and attentional impairment.

Scale for Assessment of Positive Symptoms

The SAPS consists of 30 items and 4 global ratings designed to assess the extent to which the subject manifests each of the following positive symptoms of schizophrenia: hallucinations, delusions, bizarre behavior, and positive formal thought disorder.

Symptoms on both scales are rated from absent (0) to severe (5). The ratings were based on behavior reported and/or observed during interview as well as in consultation with the patient's therapist, on behavior exhibited during the month prior to the date of the assessment.

For purposes of subtyping, schizophrenic patients were divided, initially, into three groups (Positive, Negative, and Mixed). Andreasen's criteria (Andreasen & Olsen, 1982) were used for this trichotomous grouping (see Table 1, pp. 66-67). The "Mixed" group of schizophrenics was then subdivided into those with prominent positive and negative symptoms (Both) and those without prominent symptoms (Neither), according to Andreasen's cut-off criteria, yielding a four-group (Both, n=10; Positive, n=10; Negative, n=10; Neither, n=10) rather than three-group comparison (see Appendix D). Altogether,

fourty-nine (49) schizophrenic outpatients were interviewed in order to obtain the requisite number of subjects per group (i.e., 10) necessary to carry out the four-group comparison. Subject characteristics according to these classification schema are shown in Table 2.

In subsequent data analyses, individual symptom ratings were summed to yield a general index of the overall severity of the positive or negative syndrome. This yielded two Total Scores, one for the negative scale (SANS) and one for the positive scale (SAPS). SANS and SAPS Total Scores were then used to classify subjects based on a median split (Low SANS/Low SAPS, n=10; Low SANS/High SAPS, n=10; High SANS/Low SAPS, n=10; High SANS/High SAPS, n=10) rather than an arbitrary cut-off score. This resulted in the reclassification of 15% (i.e., 6/40) of all subjects. Subject characteristics according to this reclassification are shown in Table 3.

Finally, for some of the data analyses, positive and negative symptoms were treated as categorical (i.e., present/absent) variables. This approach is consistent with the conceptualization of them as independent dimensions of symptomatology, and also allows for tests of interactive effects.

Table 2
GROUP MEANS AND STANDARD DEVIATIONS OF PATIENT CHARACTERISTICS ACCORDING TO ANDREASEN'S CRITERIA

	Schizophrenia Subtype				
Characteristic	Neither	Positive	Negative	Both	Mixed+
N	10	10	10	10	20
Age (yrs.)					
Mean	33.40	31.30	41.40	31.10	32.25
SD	5.76	6.63	9.71	5.74	5.72
Education (yrs.)					
Mean	12.80	10.80	11.70	9.90	11.35
SD	2.62	1.81	3.02	2.73	3.00
Estimated Premorbid IQ*					
Mean	108.80	99.00	105.00	98.60	103.70
SD	12.15	6.73	8.65	10.51	12.23
Handedness					
Right/Left	10/0	10/0	9/1	9/1	19/1
Sex					
Males/Females	8/2	8/2	9/1	10/0	18/2
SANS					
Mean	17.80	13.20	41.30	49.20	33.50
SD	7.93	7.36	12.41	17.55	20.86
SAPS					
Mean	7.00	35.70	5.80	32.20	19.75
SD	12.33	15.92	5.67	14.89	18.60

* Since schizophrenia always involves, by definition, deterioration from a previous level of functioning, an estimate of premorbid intelligence was calculated using a demographically-based index in the manner according to Barona, Reynolds and Chastain (1984).

\+ The "Mixed" group is the average of "Neither" and "Both" subtypes and does not constitute a distinct category. The data are included for interest only and are not included in any of the analyses.

Table 3
GROUP MEANS AND STANDARD DEVIATIONS
OF PATIENT CHARACTERISTICS BASED ON
A MEDIAN SPLIT OF SANS/SAPS RATINGS

	Schizophrenia Subtype			
	LO SANS		HI SANS	
Characteristic	LO SAPS	HI SAPS	LO SAPS	HI SAPS
N	10	10	10	10
Age (yrs.)				
Mean	36.30	29.30	41.70	29.80
SD	7.90	3.13	8.50	4.69
Education (yrs.)				
Mean	11.90	11.00	12.00	10.30
SD	3.21	1.83	2.94	2.71
Estimated Premorbid IQ				
Mean	106.10	99.80	106.40	99.10
SD	13.98	6.41	7.73	10.55
Handedness				
Right/Left	10/0	10/0	9/1	9/1
Sex				
Males/Females	8/2	8/2	9/1	10/0
SANS				
Mean	16.00	14.90	44.70	48.60
SD	8.69	6.45	10.97	16.57
SAPS				
Mean	5.20	38.70	4.90	32.80
SD	5.35	14.24	5.45	14.54

ii. Neuropsychological Battery

All subjects were administered a battery of neuropsychological tests. Testing was generally carried out immediately following the structured psychiatric interview. The 14 tests composing the battery were selected for their sensitivity to neurological dysfunction, for their careful standardization and the availability of normative data. The neuropsychological battery was selected with attention to the recommendations of Erikson and Binder (1986), who emphasized brevity, convenience, face validity, and cost effectiveness. For ease of reference, the tests and the scores used as dependent variables are described, in alphabetical order, below.

Babcock Story Recall Test (BSRT)

(Babcock, 1930)

A short (21 unit) story is read to the subject along with instructions to listen carefully and to repeat as much of the story as he/she can remember. The total number of units remembered is the Immediate Recall score. The subject is then informed that in a little while he/she will again be asked to tell back as much of the story as he/she can still remember. The story is then read for a second time. A Delayed Recall score is obtained based on the number of units the subject retains after approximately 20 minutes of testing. The subject's scores on the BSRT are the number of units correctly recalled on the Immediate and Delayed Recall trials (see Lezak, 1983, pp. 437-439).

Block Span (BS)

(Milner, 1971)

The materials for this test are nine 1.5 inch cubes fastened in random order to a black board. The examiner

taps the blocks in a pre-arranged sequence, that is from 3 to 9 blocks long and the subject must attempt to copy the tapping pattern. The test is discontinued when the subject fails two sequences at the same level (see Lezak, 1983, pp. 453-454). The score is the number of blocks in the longest sequence correctly recalled.

Category Test (CT)

(Halstead, 1947)

In this test, the stimulus figures making up the 208 items are projected on a screen. Six sets of items, each organized on the basis of a specific principle, are followed by a seventh set made up of previously shown items. The subject's task is to figure out the principle governing each set and signal the answer by pressing the appropriate key on a simple keyboard consisting of four keys. A pleasant chime rewards correct answers; errors are followed by a buzzer. The score is the number of errors (Reitan & Wolfson, 1985)

Continuous Performance Test (CPT)

(Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956)

In this test, the subject listens to a random series of spoken letters presented at one-second intervals over three minutes. The stimuli are presented by a tape recording. The subject is instructed to press a key every time he/she hears the letter "A" followed by the letter "X". The score is the number of correct responses out of a possible 45.

Controlled Word Association (Verbal Fluency)

(Benton, 1968; Benton & Hamsher, 1976)

The test consists of three word-naming trials. The examiner asks the patient to say as many words as he/she can think of that begin with a given letter of the alphabet (e.g., F-A-S), excluding proper nouns, numbers, or the same word with a different suffix. The score is the sum of all acceptable words produced in three one-minute trials (see Lezak, 1983, pp. 330-332).

Finger Tapping Test (FTT)

(Halstead, 1947)

This test uses a manual tapper to measure finger-tapping speed. The precise characteristics of this

apparatus have been standardized and maintained to ensure comparability of data between subjects and investigations (Reitan & Wolfson, 1985). The score on the FTT is based on the mean of five 10-second trials. If five consecutive trials within a range of five were obtained, the score is the mean of those trials. In the event that this criterion is not met, the score is based on the mean of the five best trials to a maximum of ten. Separate scores are computed for both dominant (D) and non-dominant (ND) hands. Hand preference is determined by the examiner from the hand used for signing the consent form.

Finger Agnosia

(Reitan & Wolfson, 1985)

This procedure tests the subject's ability to identify the individual fingers on each hand following tactile stimulation of each finger. The test is performed with the eyes closed. The subject is given a total of 20 trials on each hand. The score is recorded as the number of errors for each hand (Reitan & Wolfson, 1985, p. 34).

Rey Auditory Verbal Learning (RAVL)

(Rey, 1964; Taylor, 1959)

The test consists of five presentations, each followed by immediate spoken recall, of a 15-word list, one presentation of a second 15-word list, and a sixth recall trial. The words are presented at a rate of 1 per second. The score is the sum of words recalled on Trials I-V. (See Lezak, 1983, pp. 422-429).

Rey-Osterrieth Complex Figure (Rey-O)

(Rey, 1941; Osterrieth, 1944)

The subject is given a blank typewriter-size piece of paper, a pencil, and is instructed to copy a complex geometrical figure. After a 20-minute delay the subject is asked, without having been forewarned, to draw as much of the figure as he/she can recall. The two drawings are scored according to criteria developed by Taylor (1959). The maximum score for each drawing is 36.

Seashore Rhythm Test (SRT)

(Halstead, 1947)

This test requires the patient to discriminate between like and unlike pairs of musical beats. The

patient listens to pairs of rhythmic sequences, presented by tape recording, and indicates in writing whether each pair is the same or whether it is different. The test consists of 30 trials. The score is the number of errors (Reitan & Wolfson, 1985).

Speech Perception Test (SPT)

(Halstead, 1947)

In this test, 60 sets of four nonsense syllables beginning and ending with diferent consonants, but based on the vowel sound "ee", comprise the items, which are presented by tape recording. The subject underlines the perceived speech sound on a multiple-choice form. The score is the number of errors (Reitan & Wolfson, 1985).

Tactual Performance Test (TPT)

(Halstead, 1947)

In this test, the subject is blindfolded and asked to fit blocks onto a form board. Three trials are given, the first two with the preferred and non-preferred hands, respectively, and the third with both hands. The score for each trial is based on the time required for completion recorded in blocks per minute. Their sum is the Total Time score. Subsequently, the board is concealed, the blindfold removed, and the subject is asked, without warning, to draw the board from memory, indicating the shapes and their placement relative to one another. The drawing generates two scores. The Memory score is the number of shapes (maximum = 10) reproduced with reasonable accuracy. The Location score is the number of blocks drawn in proper relationship to other blocks on the board (maximum = 10) (Reitan & Wolfson, 1985).

Trailmaking Test (TMT)

(Reitan, 1955)

The subject must first draw lines to connect consecutively numbered circles on one worksheet (Trails A) and then connect the same number of consecutively numbered and lettered circles on another worksheet by alternating between the two sequences (Trails B). The score is the total time (in seconds) required to complete each task (Reitan & Wolfson, 1985).

Wechsler Adult Intelligence Test-Revised (WAIS-R)

(Wechsler, 1981)

This test consists of six Verbal and five Performance subtests comprising a general survey of cognitive and intellectual functions. Within each subtest, the items are arranged in order of increasing difficulty, so that a particular subtest is discontinued when the subject fails a specified number of items in succession. Raw scores are converted to a standard score (mean = 10, standard deviation = 3). By adding these Scaled Scores, three types of intelligence quotients (I.Q.'s) can be obtained: A Verbal I.Q. (VIQ) based on the sum of scaled scores on the six Verbal subtests, a Performance I.Q. (PIQ) based on the sum of scaled scores on five Performance subtests, and a Full Scale I.Q. (FSIQ) based on the sum of all 11 subtests (for a description of each subtest see Lezak, 1983). These I.Q. scores are expressed as numbers on a standard score scale (mean = 100, standard deviation = 15). Four Verbal and four Performance subtests were used and pro-rated I.Q.'s were calculated. The specific subtests are listed in Appendix B.

Subjects were tested in a private room by a trained psychometrist. The tests were administered in the following order: WAIS-R (selected subtests), Block Span, Category Test, Continuous Performance Test, Babcock Story Recall (Immediate), Speech Perception Test, Seashore Rhythm Test, Babcock Story Recall (Delayed), Controlled Word Association, Rey-Auditory Verbal Learning (with Recognition List), Rey Osterrieth Complex Figure (Copy), Finger Tapping Test, Finger Agnosia, Rey Osterrieth Complex Figure (Delayed Recall), and the Tactual Performance Test. The neuropsychological battery took, on average 3-4 hours per subject to complete.

iii. Impairment Indicies

In order to assess degree of overall impairment of intellectual functions and general adaptive abilities the

following global indicies were utilized.

Halstead Impairment Index

(Reitan & Wolfson, 1985)

The Halstead Impairment Index is a summary measure based on seven measures, from the Halstead-Reitan Neuropsychological Battery, considered optimally sensitive to organic brain dysfunction. The seven measures are the Category Test, Finger Tapping Test (Dominant Hand), Tactual Performance Test (Total Time, Memory, Location), Speech Perception Test and Seashore Rhythm Test. The impairment index is based on the proportion of tests which have results in the range characteristic of brain damaged subjects. Customarily, normal subjects obtain impairment indicies that range between 0.00 and 0.3; 0.4 is a borderline score; and 0.5 to 1.0 characterizes subjects with impaired brain functions.

Deterioration Index

A Deterioration Index was obtained by subtracting the actual WAIS-R, Full Scale I.Q score of each subject from a demographically derived estimate of premorbid intelligence for the WAIS-R (Barona et al., 1984). Demographic information used in the estimation of premorbid intellectual functioning are age, sex, race, education and highest occupational attainment. The deterioration index is expressed in terms of I.Q. points.

iv. Behavioral Rating Scale

A behavioral rating scale was included to estimate quality of life and performance of basic roles based on self-report.

Social Adjustment Scale (SAS)

(Weissman & Bothwell, 1976)

A 54 item self-report questionnaire designed to assess functioning in the domains of employment, leisure time, family relations and finances. The SAS was completed by the subject. Individual items were rated from 0 (normal adjustment) to 5 (severe maladjustment). Since not all items applied to all subjects scores were prorated on a percentage basis. SAS total scores ranged from .00 to 1.00 where higher scores reflect increasing impairment.

Statistical analyses of the data were carried out using BMDP software on a microcomputer (IMB PC).

RESULTS

Hypothesis 1

In order to test the hypothesis that cognitive impairment is characteristic of negative- but not positive-symptom schizophrenia, data were first analysed using symptom ratings as discrete variables according to Andreasen and Olsen's (1982) conceptualization of the symptom complexes. After subtyping according to Andreasen and Olsen's (1982) criteria (i.e., Positive, Negative, Mixed) schizophrenics who showed mixed symptomotology were further subdivided into those who showed either both or neither sets of symptoms according to the positive/negative distinction to yield a four-group comparison (Both, n=10; Positive, n=10; Negative, n=10; Neither, n=10).

Group means and standard deviations of demographic variables were previously reported (see Table 2; p. 86). The sample was comprised, overwhelmingly, of right-handed (38:2) males (35:5). Demographic characteristics of the four schizophrenia subtypes were analyzed by one-way analysis of variance (ANOVA); among demographic variables (age, education, estimated premorbid intelligence, handedness, and gender) significant group differences were

observed for age $F(1,39)= 4.60$, $p<.01$. Mean comparisons (two-tailed) using the T-Method (Glass & Stanley, 1970) found subjects with prominant negative symptoms to be significantly older than those with positive symptoms or with both positive and negative symptoms ($p<.05$). Subtypes were then compared on the basis of several global neuropsychological (Halstead Impairment Index, Deterioration Index) and composite cognitive (Wechsler Verbal, Performance and Full Scale I.Q. Scores) indicies.

In order to control statistically for the effects of age on test performance, Analysis of Covariance (ANCOVA) was conducted on the neuropsychological variables using "age" as the covariate. Analysis of variance (ANOVA) was conducted on Wechsler Scales (Verbal, Performance, Full Scale I.Q.) as these measures are already adjusted for age according to age-based norms. Where F-ratios significant at the .05 level or greater were obtained, multiple comparison procedures were employed. When the number of observations for each group was equal, the T-method (Tukey) was used, and when unequal the S-method (Scheffe) of multiple comparisons was applied for all possible contrasts between means (i.e., ANOVA) or adjusted means (i.e., ANCOVA) according to the procedures outlined in Glass and Stanley (1970).

In general, the results of one-way ANCOVA of scores on the Halstead Impairment Index and Deterioration Index

were not statistically significant, suggesting that all groups are fairly comparable in terms of their overall level of neuropsychological functioning. Comparisons between subtypes on Wechsler Intelligence Scales revealed significant overall F values for Wechsler Verbal I.Q., $F(3,36)= 3.05$, $p<.05$; Performance I.Q., $F(3,36)= 3.60$, $p<.05$ and Full Scale I.Q., $F(3,36)= 4.06$, $p<.05$. The results of mean group comparisons for all possible contrasts revealed several significant differences with the Neither subgroup showing significantly higher Verbal, [$F(3,39)= 4.28$, $p<.05$ (two-tailed)], Performance, [$F(3,39)= 4.00$, $p<.05$ (two-tailed)], and Full Scale [$F(3,39)= 4.77$, $p<.05$ (two-tailed)] I.Q. scores than positive-symptom schizophrenics as well as significantly higher Performance [$F(3,39)= 3.72$, $p<.05$ (two-tailed)], and Full Scale [$F(3,39)= 3.17$, $p<.05$ (two-tailed)] I.Q. scores than schizophrenics with both positive and negative symptoms (Both). Thus, comparisons on several and various global indices of cognitive and neuropsychological impairment consistently failed to differentiate among schizophrenics with positive versus negative symptoms (see Table 4). These findings do not generally support the hypothesis that cognitive impairment is characteristic of negative- and not positive-symptom schizophrenia. In fact, positive-symptom schizophrenics showed significantly lower I.Q. scores relative to the asymptomatic subtype, whereas both

Table 4

ANOVA/ANCOVA OF GLOBAL INDICIES OF COGNITIVE AND NEUROPSYCHOLOGICAL IMPAIRMENT AMONG SCHIZOPHRENICS SUBTYPED ACCORDING TO ANDREASEN'S CLASSIFICATION SCHEMA

	Schizophrenia Subtype						
Measure	Neither (A)	Pos. (B)	Neg. (C)	Both (D)	F	p	Pattern
N	10	10	10	10			
Halstead Impairment Index							
Mean	.36	.61	.61	.60	1.94	n.s.	A=B=C=D
SD	.20	.29	.29	.26			
Deterioration Index							
Mean	-13.30	-12.70	-10.80	-12.00	0.11	n.s.	A=B=C=D
SD	7.78	6.73	8.43	8.68			
Verbal IQ							
Mean	98.30	81.60	91.20	89.10	3.05	<.05	A>B
SD	19.23	9.80	9.33	8.18			
Performance IQ							
Mean	93.20	83.00	89.30	83.70	3.60	<.05	A>B=D
SD	8.26	7.23	10.09	6.17			
Full Scale IQ							
Mean	95.50	80.90	89.60	85.80	4.06	<.05	A>B=D
SD	3.83	4.24	10.28	6.48			

both positive- and negative-symptom schizophrenics showed, overall, mild/moderate neuropsychological impairment and a 10-12 point drop in Full Scale I.Q. from estimated premorbid functioning. The results of the present study do not therefore support Andreasen's position that cognitive impairment is uniquely associated with negative-symptom schizophrenia.

In an effort to seek additional support for present findings, data were reanalyzed following the reclassification of subjects based on a median split of SANS and SAPS ratings (Low SANS/Low SAPS; n=10, Low SANS/High SAPS; n=10, High SANS/Low SAPS; n=10, High SAPS/High SANS; n=10) rather than Andreasen's arbitrary cut-off. This resulted in the reassignment of 15% (i.e., 6/40) of all subjects. One-way ANOVAS performed on demographic variables again revealed a significant group difference in age [$F(1,39)= 8.33$, $p<.01$]. Mean comparisons found subjects with High SANS/Low SAPS ratings to be significantly older ($p<.05$) than subjects in the High SAPS/Low SANS or High SAPS/High SANS subgroups. ANCOVA (see Table 5) results suggested that reclassification did not substantially affect outcome; again, no significant group differences in overall cognitive and neuropsychological functioning were observed between positive- and negative-symptom schizophrenics. Thus, the negative findings appear unrelated to Andreasen's somewhat

Table 5

ANOVA/ANCOVA OF GLOBAL INDICIES OF COGNITIVE AND NEUROPSYCHOLOGICAL IMPAIRMENT AMONG SCHIZOPHRENICS SUBTYPED ACCORDING TO MEDIAN SPLIT OF SANS/SAPS RATINGS

	Schizophrenia Subtype					
Measure	LO SANS LO SAPS	LO SANS HI SAPS	HI SANS LO SAPS	HI SANS HI SAPS	F	p
N	10	10	10	10		
Halstead Impairment Index						
Mean	.56	.54	.56	.57	0.01	n.s.
SD	.30	.28	.33	.22		
Deterioration Index						
Mean	-13.10	-13.90	- 9.20	-12.60	0.42	n.s.
SD	8.25	14.01	8.13	9.03		
Verbal IQ						
Mean	94.60	82.20	93.90	89.50	1.94	n.s.
SD	20.03	9.87	10.31	8.00		
Performance IQ						
Mean	88.70	84.80	92.40	83.30	2.37	n.s.
SD	8.87	8.52	9.49	6.41		
Full Scale IQ						
Mean	91.70	81.80	92.60	85.70	2.53	n.s.
SD	14.47	8.19	9.50	6.88		

arbitrary system of classification.

Hypothesis 2

Andreasen's criteria were again used, in this instance to examine patterns of neuropsychological deficit among subtypes of schizophrenia in order to address the question of whether qualitative rather than quantitative differences in neuropsychological performance exist between subtypes as suggested by Green and Walker (1985).

The results of ANCOVAS carried out on neuropsychological variables (see Table 6) revealed significant overall F values for Trails A [$F(3,34)= 2.95$, $p=.05$], Rey Auditory Verbal Learning [$F(3,35)= 3.53$, $p=.03$], Controlled Word Association (Verbal Fluency) [$F(3,34)= 4.49$, $p=.009$], Digit Span (Digits Backward) [$F(3,35)= 4.83$, $p= .006$], Babcock Story Recall (Delayed Recall) [$F(3,35)= 3.27$, $p=.03$], and Category Test [$F(3,35)= 2.86$, $p=.05$].

The results of mean comparisons revealed that significant differences in neuropsychological performance, when found, separated the "Neither subtype" from the other three schizophrenic subtypes (Positive, Negative, and Both) with the Neither subgroup performing relatively better. No neuropsychological variable discriminated positive- from negative-symptom schizophrenics. Schizophrenics in the Neither subgroup performed significantly better than

Table 6

ANCOVA OF NEUROPSYCHOLOGICAL MEASURES AMONG SCHIZOPHRENICS SUBTYPED ACCORDING TO ANDREASEN'S CLASSIFICATION SCHEMA

	Schizophrenia Subtype						
Measure	Neither	Pos.	Neg.	Both	Mixed+	F	p
N	10	10	10	10	20		
Category Test							
Mean	50.40	70.50	62.20	77.90	64.15	2.86	.05
SD	22.39	21.62	24.40	23.47			
Speech Perception Test							
Mean	2.50	5.60	6.70	5.40	3.55	1.38	n.s.
SD	2.12	3.57	6.34	5.13			
Seashore Rhythm Test							
Mean	4.70	5.80	6.30	5.50	5.10	0.31	n.s.
SD	4.68	3.72	2.35	3.94			
Finger Tapping (D)							
Mean	49.00	46.22	44.40	44.40	46.70	1.04	n.s.
SD	4.99	7.49	9.57	8.95			
Finger Tapping (ND)							
Mean	46.50	43.00	40.00	42.25	44.38	1.57	n.s.
SD	3.83	4.24	10.28	6.48			
Finger Agnosia (D)							
Mean	1.00	0.44	1.11	2.20	1.60	1.30	n.s.
SD	1.88	0.53	3.83	1.63			
Finger Agnosia (ND)							
Mean	1.00	0.50	1.00	2.10	1.55	1.59	n.s.
SD	1.32	0.53	1.50	3.18			

Table 6 (con't)

	Schizophrenia Subtype						
Measure	Neither	Pos.	Neg.	Both	Mixed+	F	p
TPT (Blocks/Min.)							
Mean	2.04	1.62	1.21	1.71	1.88	0.48	n.s.
SD	0.79	0.73	0.94	1.07			
TPT (Memory)							
Mean	6.78	6.44	5.10	5.40	6.09	1.76	n.s.
SD	0.67	1.13	2.56	1.84			
TPT (Location)							
Mean	3.11	2.44	2.60	2.30	2.71	0.41	n.s.
SD	1.90	1.42	2.41	1.70			
Trails A (sec.)							
Mean	27.56	38.56	47.10	36.60	32.08	2.95	.04
SD	9.36	10.10	19.02	9.11			
Trails B (sec.)							
Mean	60.00	92.89	123.00	101.90	80.95	2.47	n.s.
SD	26.50	44.60	59.27	65.94			
Rey-Osterrieth Complex Figure (copy)							
Mean	34.00	29.00	32.00	29.85	31.92	0.98	n.s.
SD	2.50	5.46	2.16	3.74			
Rey-Osterrieth Complex Figure (recall)							
Mean	17.72	14.56	15.50	13.40	15.56	0.69	n.s.
SD	8.48	27.22	7.35	5.94			
Rey Auditory Verbal Learning							
Mean	47.44	31.60	37.80	36.30	41.87	3.53	.02
SD	8.14	12.08	11.17	10.56			

Table 6 (con't)

	Schizophrenia Subtype						
Measure	Neither	Pos.	Neg.	Both	Mixed+	F	p
Verbal Fluency							
Mean	42.22	30.67	23.00	31.50	36.85	4.49	.009
SD	9.61	7.26	8.50	7.46			
Continuous Performance Test							
Mean	2.89	7.90	10.30	8.30	5.60	1.33	n.s.
SD	3.41	9.56	7.54	9.31			
Block Span							
Mean	5.60	4.90	5.20	4.70	5.15	2.20	n.s.
SD	.70	.88	.92	.67			
Digits Forward							
Mean	6.90	5.70	5.90	6.20	6.55	2.22	n.s.
SD	1.10	0.95	0.74	0.92			
Digits Backward							
Mean	5.10	4.30	3.80	3.80	4.45	4.83	.006
SD	1.10	0.48	1.03	0.79			
Babcock (Immed.)							
Mean	8.95	7.50	9.20	6.85	7.90	0.38	n.s.
SD	3.44	3.24	4.60	7.50			
Babcock (Delay)							
Mean	13.35	8.55	11.65	9.05	11.20	3.27	.04
SD	3.12	3.83	5.85	5.48			

+ Not included in the data analyses

positive-symptom schizophrenics on Babcock Story Recall (Delayed Recall) [$F(3,39)= 4.20$, $p<.05$ (two-tailed)], the Rey Auditory Verbal Learning Test [$F(3,39)= 3.15$, $p<.05$ (two-tailed)], and Wechsler Verbal [$F(3,39)= 4.28$, $p<.05$ (two-tailed)], Performance [$F(3,39)= 4.00$, $p<.05$ (two-tailed)] and Full Scale [$F(3,39)= 4.77$, $p<.05$ (two-tailed)] I.Q. measures, negative-symptom schizophrenics on Controlled Word Association (Verbal Fluency) [$F(3,39)= 4.35$, $p<.05$ (two-tailed)] and Digit Span (Digits Backward) [$F(3,39)= 4.95$, $p<.05$ (two-tailed)], and positive and negative-symptom (Both) schizophrenics on the Category Test [$F(3,39)= 3.44$, $p<.05$ (two-tailed)], Digit Span (Digits Backward), $F(3,39)= 4.50$, $p<.05$ (two-tailed)] and Wechsler Performance [$F(3,39)= 3.72$, $p<.05$ (two-tailed)] and Full Scale [$F(3,39)= 3.17$, $p<.05$ (two-tailed)] I.Q. measures.

Significant differences on various neuropsychological tests, based on Andreasen's subtyping criteria, tended to distinguish, almost invariably, schizophrenics with proportionately few symptoms (Neither) from other schizophrenic subtypes. The other symptomatic subtypes (Positive, Negative, and Both) were largely indistinguishable based on level-of-performance comparisons across a wide range of neuropsychological measures. On the other hand, significant group differences, when found, suggested an association between positive symptoms and a

tendency to do poorly (in relation to the relatively asymptomatic subgroup) on tests which, purportedly, tap functions subserved by the left hemisphere. These deficits included, but were not limited to, impaired performance on tests of verbal reasoning and problem-solving ability (Verbal I.Q.), as well as verbal learning (Rey-Auditory Verbal Learning) and verbal memory (Babcock Story Recall, Delayed Recall). This pattern is consistent, but more expansive, than the pattern of deficits reported by Green and Walker (1985) who observed an association between positive symptoms and deficient verbal memory. On the other hand Green and Walker also observed an association between negative symptoms and visual-spatial deficits, a pattern which was not replicated here. Rather, negative-symptom schizophrenics appeared to perform poorer on tests which purportedly tap, among other abilities, verbal fluency and productivity (Controlled Word Association) as well as the ability to manipulate verbal information in short-term memory (Digit Span, Digits Backward).

Data were again reanalyzed following the reclassification of subjects according to a median split of SANS/SAPS ratings (see Table 7). One-way ANCOVA (using age as the covariate) revealed a significant overall F value for Controlled Word Association (Verbal Fluency) [$F(3,34) = 4.49$, $p=.009$], although means comparisons using Scheffe's

Table 7

ANCOVA OF NEUROPSYCHOLOGICAL MEASURES AMONG SCHIZOPHRENICS SUBTYPED ACCORDING TO MEDIAN SPLIT OF SANS/SAPS RATINGS

	Schizophrenia Subtype					
Measure	LO SANS LO SAPS	LO SANS HI SAPS	HI SANS LO SAPS	HI SANS HI SAPS	F	p
N	10	10	10	10		
Category Test						
Mean	58.80	64.80	65.20	72.20	0.69	n.s.
SD	28.13	21.62	29.37	22.24		
Speech Perception Test						
Mean	4.40	5.00	6.20	4.83	0.59	n.s.
SD	4.74	3.43	5.94	4.84		
Seashore Rhythm Test						
Mean	5.90	5.40	5.80	5.20	0.07	n.s.
SD	4.68	3.72	2.35	3.94		
Finger Tapping (D)						
Mean	46.50	47.44	42.20	46.00	0.28	n.s.
SD	6.24	4.39	10.27	8.07		
Finger Tapping (ND)						
Mean	43.86	43.14	39.00	43.00	0.82	n.s.
SD	5.96	2.73	9.38	6.09		
Finger Agnosia (D)						
Mean	1.30	0.55	2.22	1.00	0.43	n.s.
SD	1.88	0.53	3.83	1.63		
Finger Agnosia (ND)						
Mean	0.90	0.66	2.11	1.10	0.70	n.s.
SD	1.29	0.50	3.30	1.60		

Table 7 (con't)

Measure	Schizophrenia Subtype: LO SANS LO SAPS	LO SANS HI SAPS	HI SANS LO SAPS	HI SANS HI SAPS	F	p
TPT (Blocks/Min.)						
Mean	1.67	2.62	1.23	1.74	0.51	n.s.
SD	0.87	2.69	1.00	1.05		
TPT (Memory)						
Mean	6.30	6.55	5.50	5.40	1.04	n.s.
SD	1.42	1.01	2.50	1.84		
TPT (Location)						
Mean	2.40	2.44	3.10	2.30	1.48	n.s.
SD	1.96	1.42	2.33	1.70		
Trails A (sec.)						
Mean	36.50	32.77	43.00	35.10	0.71	n.s.
SD	19.63	7.31	16.91	7.77		
Trails B (sec.)						
Mean	98.80	78.44	124.33	82.30	0.14	n.s.
SD	73.64	17.06	71.01	16.20		
Rey-Osterrieth Figure (copy)						
Mean	32.25	39.64	32.00	30.05	1.22	n.s.
SD	3.98	21.39	2.62	3.56		
Rey-Osterrieth Figure (recall)						
Mean	15.80	23.44	16.90	13.05	0.83	n.s.
SD	8.48	27.22	7.35	5.94		
Rey Auditory Verbal Learning						
Mean	39.40	35.78	41.10	36.70	1.06	n.s.
SD	13.36	11.79	11.37	10.24		

Table 7 (con't)

Measure	Schizophrenia Subtype: LO SANS LO SAPS	LO SANS HI SAPS	HI SANS LO SAPS	HI SANS HI SAPS	F	p
Verbal Fluency						
Mean	39.40	31.11	24.30	31.40	4.49	.009
SD	10.71	7.41	10.30	7.52		
Continuous Performance Task						
Mean	39.00	39.60	33.70	38.20	0.42	n.s.
SD	8.52	6.50	7.86	8.77		
Block Span						
Mean	5.40	4.90	5.40	4.70	2.05	n.s.
SD	.84	.88	.84	.67		
Digits Forward						
Mean	6.33	5.80	6.20	6.10	0.68	n.s.
SD	1.22	0.79	0.63	0.99		
Digits Backward						
Mean	4.60	4.30	4.20	3.90	0.88	n.s.
SD	1.26	0.48	1.32	0.74		
Babcock (Immed.)						
Mean	8.65	7.05	9.95	6.90	0.51	n.s.
SD	3.65	3.16	4.29	4.50		
Babcock (Delay)						
Mean	12.20	8.40	13.30	8.95	1.48	n.s.
SD	4.69	4.02	4.74	5.62		

procedure did not reveal any significant group differences. These findings suggest that different subtyping criteria may yield markedly different patterns of neuropsychological test results (see Table 8).

SANS and SAPS ratings were also analyzed as categorical (i.e., present/absent) variables consistent with the conceptualization of them as independent dimensions of symptomatology. This approach also allowed for tests of interactive effects. The nonsignificant correlation (r= -0.10) observed between SANS and SAPS ratings was consistent with that conceptualization. A Two-way ANCOVA was carried out using SANS and SAPS ratings as independent variables with neuropsychological test scores, I.Q. measures, and global impairment indices as dependent variables using BMDP2V analyses of variance and covariance with repeated measures.

Significant main effects and significant overall F values were observed for positive symptoms on Rey Auditory Verbal Learning [F(1,34)= 6.26, p=.04], Block Span [F(1,34)= 4.26, p=.05], Babcock Story Recall (Delayed Recall) [F(1,34)= 5.25, p=.03] and the Category Test [F(1,34)= 7.02, p=.01]. Significant main effects were also observed for negative symptoms on the Tactual Performance Test (Memory) [F(1,34)= 4.78, p=.04], Controlled Word Association (Verbal Fluency) [F(1,34)= 8.00; p=.008], and Digit Span (Digits Backward) [F(1,34)= 10.41, p=.003]. In

Table 8

MEAN COMPARISONS AMONG NEUROPSYCHOLOGICAL VARIABLES YIELDING SIGNIFICANT OVERALL MULTIVARIATE F VALUES

Measure	Schizophrenia Subtype: Neither (A)	Pos. (B)	Neg. (C)	Both (D)	Signif. Group Differ.
Verbal IQ Mean	98.30	81.60	91.20	89.10	A>B
Performance IQ Mean	93.20	83.00	89.30	83.70	A>B;A>D
Full Scale IQ Mean	95.50	80.90	89.60	85.80	A>B;A>D
Category Test Mean	50.40	70.50	62.20	77.90	A>D
Trails A Mean	27.57	38.56	47.10	36.60	None
Rey Auditory Verbal Learning Mean	47.44	31.60	37.80	36.30	A>B
Verbal Fluency Mean	42.22	30.67	23.00	31.50	A>C
Babcock (Delay) Mean	13.35	8.55	11.65	9.05	A>B
Digits Backward Mean	5.10	4.30	3.80	3.80	A>C;A>D

Measure	LO SANS LO SAPS	HI SANS HI SAPS	LO SANS HI SAPS	HI SANS LO SAPS	
Verbal Fluency Mean	39.4	31.1	24.3	31.4	None

addition, significant positive/negative symptom interactions were observed on Controlled Word Association (Verbal Fluency) [$F(1,34)= 8.93$, $p=.005$], and Digit Span (Digits Forward) [$F(1,34)= 5.21$, $p=.03$] tests. These findings were not markedly different from the pattern of results using one-way ANOVA and Andreasen's cut-off criteria, although the pattern of deficts associated with positive symptoms (impairment on tests of non-verbal as well as verbal learning and memory) relative to negative symptoms (impairment on a measure of fluency and productivity), is more conducive to a positive/posterior (temporal) versus negative/anterior (frontal) hypothesis than one based on right versus left hemisphere dysfunction.

In order to investigate the a priori hypothesis of possible lateralizing significance to deficit patterns among subtypes of schizophrenia, discriminant function analysis was performed using the nine symptom rating subscales from the SANS and SAPS as independent (predictor) variables and the Reitan Laterality Index (Reitan, 1986) based on T.P.T performance as the dependent (outcome) variable (see Table 9). SPSS/PC+ Stepwise Discriminant function analysis was selected in order to delete symptom variables which were not useful in discriminating among groups. Of the 40 cases, 1 was dropped due to incomplete data, and 2 did not yield lateralized findings and were not included in the data analysis. The discriminant function,

with a combined Chi Square [(9) = 7.14, p=.62], was not statistically significant. No symptom variable or combination of symptoms therefore adequately discriminated between schizophrenics showing neuropsychological evidence of lateralized cortical dysfunction.

Table 9

FREQUENCY OF LATERALIZED IMPAIRMENT ON THE T.P.T AMONG SCHIZOPHRENIC SUBTYPES

	Left Hemisphere Dysfunction				Right Hemisphere Dysfunction		
	Sev.	Mod.	Mild	None	Mild	Mod.	Sev.
Positive/ Both	[10	0	0]	1	[1	1	6]
		[10]				[8]	
Negative/ Both	[9	1	0]	1	[0	2	7]
		[10]				[9]	

p= .62

In order to investigate the a posteriori hypothesis that subtle differences between subtypes in neuropsychological test performance can be accounted for on the basis of factors other than right-left differences, the 19 neuropsychological variables were ranked according to their: (a) sensitivity to anterior versus posterior dysfunction and, (b) cognitive complexity, by three practicing clinical neuropsychologists. Rank order was determined by averaging the ratings of two

neuropsychologists and using the third rating to break ties. Spearman rank-order coefficients were obtained using F-ratios for the main effects of neuropsychological variables and rankings according to anterior versus posterior and task complexity dimensions, however neither of these coefficients approached statistical significance ($p>.05$). Thus, it was concluded that no significant relationship appears to exist between positive and/or negative symptoms of schizophrenia and patterns of neuropsychological performance which suggest more generalized, lateralized or localized cortical dysfunction.

Hypothesis 3

In order to test the hypothesis that attentional deficits are unique to negative-symptom schizophrenia correlations between schizophrenic subtypes, the Attention subscale of the SANS, and objective, neuropsychological measures of attention were examined. The neuropsychological measures included Digit Span (Digits Forward, Digits Backward), Block Span, WAIS-R Digit Symbol, Seashore Rhythm Test, Trailmaking Tests (Trails A/B) and the Continuous Performance Test (see Appendix B). Attentional capacity is considered a major contributing skill in the performance of each of these tasks (Solhberg & Mateer, 1989).

Among the eight neuropsychological measures of

attention a significant group difference in level of performance was observed only on the Digits Backward subtest (previously reported). The results of mean comparisons further revealed that schizophrenics without prominent symptoms (Neither) perform better than negative-symptom schizophrenics (Negative) and schizophrenics with prominent positive and negative symptoms (Both). The relationship between negative symptoms and poorer performance on the Digits Backward subtest generally held regardless of whether the symptom ratings were analyzed as continuous or discrete variables; however, the results of additional level-of-performance comparisons suggest that, viewed in relation to external normative criteria (see Table 10), negative-symptom schizophrenics show, on average, only borderline impaired performance on Digits Backward. Based on similar comparisons there is also some suggestion that, overall, negative-symptom schizophrenics may show deficient performance on tests (Trails A/B) in which attention is tapped in the context of simple information processing (Sohlberg & Mateer, 1989). Thus, it would appear that negative symptoms may be related to deficient, or at least poorer, performance on attention tasks involving immediate or working memory (Digits Backward) and, possibly, simple information processing as well. While the relationship between the deficits reported here and the difficulties in

sustained attention reported by Green and Walker (1986a) is unclear, both studies support the general position that negative symptoms appear to be associated with attentional impairment, although attentional deficits do not appear to be unique characteristics of negative-symptom schizophrenia.

On the other hand, positive symptoms were also associated with poorer performance on the Block Span task (previously reported), although the clinical significance of this finding is questionable. Based on comparisons with external normative criteria, the mean test score on Block Span for the positive-symptom group reflected borderline impairment and was not readily distinguishable from other subgroups in this regard.

In summary, the results of performance comparisons between schizophrenic subtypes on varied attentional tasks revealed proportionately few significant group differences; however, differences, when found, appear to be qualitatively different for positive- than for negative-symptom schizophrenia. In generally, the data do not support the hypothesis that attention deficits are uniquely associated with negative symptoms of schizophrenia.

The relationship between objective (psychometrist) and subjective (interviewer) ratings of attention was also examined. It was found that among neuropsychological

Table 10

LEVEL OF PERFORMANCE COMPARISONS BETWEEN SCHIZOPHRENIC SUBTYPES ON ATTENTION TASKS IN RELATION TO NORMATIVE DATA

	Schizophrenia Subtype				
Measure	Neither	Pos.	Neg.	Both	Normal
Digits Forward [1]					
Mean	6.9	5.7	5.9	6.2	8.7 (1.8)
Percentile	16th	5th	7th	8th	50th
Range	L.A.	Bdl.	Bdl.	Bdl.	Average
Digits Backward [2]					
Mean	5.1	4.3	3.8	3.8	6.8 (2.1)
Percentile	22nd	12th	8th	8th	50th
Range	L.A.	L.A.	Bdl.	Bdl.	Average
Block Span [2]					
Mean	5.6	4.9	5.2	4.9	8.6 (1.8)
Percentile	5th	2nd	3rd	2nd	50th
Range	Bdl.	Bdl.	Bdl.	Bld.	Average
Digit Symbol [1]					
Mean	8.4	6.5	5.8	5.5	9.8 (3.3)
Percentile	34th	15th	11th	9th	50th
Range	Avg.	L.A.	L.A.	L.A.	Average
Seashore Rhythm [3]					
Mean	4.7	5.8	6.3	5.5	2.3 (2.1)
Percentile	13th	5th	3rd	7th	50th
Range	L.A.	Bdl.	Bdl.	Bld.	Average
Trails A [3]					
Mean	27.6	38.6	47.1	36.6	27.5 (8.3)
Percentile	50th	9th	1st	14th	50th
Range	Avg.	L.A.	Imp.	L.A.	Average
Trails B [3]					
Mean	60.0	92.9	123.0	101.9	62.1 (17.5)
Percentile	55th	4th	<1st	<1st	50th
Range	Avg.	Bdl.	Imp.	Imp.	Average
Continuous Performance Test					
Mean	2.9	7.9	10.3	8.3	1-2

[1] (Wechsler, 1981) [2] (Wechsler, 1987) [3] (Fromm-Auch & Yeudall, 1983)

Avg.=Average; L.A.=Low Average; Bdl.=Borderline; Imp.=Impaired.

measures of attention only Digits Backward ($r= 0.37$, $p<.05$, $df= 38$) and the Continuous Performance Test ($r= 0.36$, $p<.05$, $df= 38$) correlated significantly with the attention rating obtained from psychiatric interviews. The significant correlation between performance on the Digits Backward task and the attention rating was perhaps predictable, since the attention ratings are made, according to SANS criteria, based on the subject's ability to spell the word "world" backwards. Inasmuch as negative-symptom schizophrenics appear to show relative deficits on the digits backward task, the data lend some support to the content validity of the Attentional subscale of the SANS. On the other hand, the nonsignificant correlation (.29) between SANS Attention subscale and Total Score detracts from the internal consistency of SANS. While the validity of SANS is beyond the scope of this investigation, it is worthwhile noting that Andreasen and Olsen (1982) also found attentional impairment ratings were not significantly correlated with other negative symptom ratings. Moreover, Walker et al. (1988) found attentional impairment to be positively correlated with positive formal thought disorder as well as the SAPS Total Score. Thus the psychometric properties of the Attention subscale, in particular and SANS/SAPS rating scales in general, appear questionable and potentially detract from the validity of neuropsychological findings based on Andreasen's subtyping

criteria.

Hypothesis 4

Regression analysis was employed to determine if information regarding symptoms or combination of symptoms independent of the positive/negative symptom distinction is useful in predicting degree of neuropsychological impairment. Nine individual symptom subscales from the SANS and SAPS were used as predictor variables with Halstead Neuropsychological Impairment Index as the dependent variable. In order to control statistically for the effect of age on neuropsychological test performance, "age" was forced as the first predictor variable. Analyses were performed using BMDP2R Stepwise Regression, however the program terminated after step 1 due to insufficient F-ratio for further stepping, and R was not significantly different from zero at the end of the first step [$R = .62$, $F(1,38) = 2.39$, $p > .05$]. Individual symptom ratings therefore were insufficiently correlated with degree of neuropsychological impairment to allow for meaningful prediction.

The insignificant correlation between SANS+SAPS Total Score (as general indicator of symptom severity) and the Halstead Impairment Index (as a general indicator of neuropsychological functioning) may be taken as further

evidence for the general dissociation between neuropsychological performance and the symptom presentation of schizophrenic patients.

Post-hoc comparisons between other schizophrenic subtypes revealed that schizophrenics in the Neither group obtained a mean impairment index within normal limits (i.e., <.50), whereas other mean scores reflected mild/moderate neuropsychological impairment. Furthermore, the Neither group performed better on average than schizophrenics in other groups (Positive, Negative, Both) on all but three (Finger Agnosia, Dominant and Nondominant; Babcock Story Recall, Immediate Recall) neuropsychological measures (see Table 7). The data appear to suggest that a general relationship between symptomatic status and neuropsychological functioning may exist.

Subsequent analysis of impairment ratings, based on cut-off criteria for impairment on the Halstead-Impairment Index, between schizophrenics with and without prominent symptoms, revealed more than chance association (Fisher Exact Test; p= .04) (See Table 11). The results were taken as support for the position that schizophrenics without prominent symptoms are less likely to be neuropsychologically impaired than those with prominent symptoms, independent of the positive versus negative symptom distinction.

Table 11

FREQUENCY OF NEUROPSYCHOLOGICAL IMPAIRMENT AMONG SCHIZOPHRENICS WITH AND WITHOUT PROMINENT SYMPTOMS

		HALSTEAD IMPAIRMENT INDEX		
		Intact (<.50)	Impaired (>.50)	
SYMPTOMS	Neither	7	3	/10
	Positive Negative Both	10	20	/30
		/17	/23	/40

p= .04

DISCUSSION

The issue of heterogeneity of symptoms has been at the heart of schizophrenia research since the disorder was first described in the literature and much emphasis has been placed on the identification of meaningful subtypes within the schizophrenic domain. Over the years such distinctions as schizoaffective versus non-affective, paranoid versus non-paranoid, acute versus process, and chronic versus reactive schizophrenia have all enjoyed popularity; however, many of these classification systems have been abandoned because they offer no clinically significant aetiological, treatment or prognostic information. The search for relatively discrete subtypes of schizophrenia has now evolved to a distinction based on whether symptoms of the disorder are predominantly positive (florid) or negative (defect). With the recent recognition that schizophrenia is a brain-based disorder, part of what makes this distinction unique is that it is the first classification system based on functional brain systems and areas of brain dysfunction.

The positive versus negative symptom distinction is based on the assumption that there are (at least) two distinct syndromes in schizophrenia which differ, in

addition to symptom presentation, in terms of underlying brain pathology, neuroleptic responsivity, prognosis for recovery and neuropsychological characteristics. Specifically, Crow (1980; Crow, Ferrior & Johnstone, 1986) and Andreasen (1982; Andreasen & Olsen, 1982) have proposed a two-syndrome concept of schizophrenia in which one syndrome is characterized by a preponderance of positive symptoms (e.g., hallucinations, delusions), acute onset of illness, neuroleptic responsivity, intact cognitive functioning and a putative dopamine pathophysiology. In contrast, the other syndrome involves predominantly negative symptoms (e.g., affective flattening, avolition), a chronic course, neuroleptic nonresponsivity, cognitive and attentional impairment and a proposed pathologic process involving structural brain changes. Unfortunately, much of the support for this model has been largely indirect and researchers now question whether the two syndromes are as dichotomous as previously proposed.

The purpose of this study has been to examine, more directly and more specifically, the relationship between neuropsychological functioning and positive versus negative symptoms of schizophrenia. Specifically, it has been suggested (Crow, 1980; Andreasen, 1982) that negative-symptom schizophrenics show impaired attention and cognition, whereas positive-symptom schizophrenics are described as neuropsychologically intact. To date, support

for this position seems more intuitively rather than empirically derived; however, indirect evidence may be taken from studies that show a relationship between negative symptoms and CT abnormality (e.g., Dennert & Andreasen, 1983) which, taken in conjunction with other studies (e.g., Golden et al., 1980) that show a relationship between CT abnormality and neuropsychological impairment (Golden et al., 1980), suggest some association between negative symptoms and neuropsychological deficits. In summary, the relationship between neuropsychological performance and positive versus negative symptoms of schizophrenia was considered deserving of more direct research attention.

In the preceding study the neuropsychological characteristics of positive versus negative symptoms of schizophrenia were examined in terms of four specific hypotheses. Two of the hypotheses concerned the assumption that negative symptoms are uniquely associated with cognitive (Hypothesis 1) and attentional impairment (Hypothesis 3). Another hypothesis addressed the question of whether deficit patterns unique to positive- or negative-symptom schizophrenia, if found, were of lateralizing or localizing significance (Hypothesis 2) and, finally, the possibility that other symptom combinations, independent of the positive/negative symptom distinction are more valid predictors of neuropsychological impairment

among schizophrenics was explored (Hypothesis 4).

Overall, the general neuropsychological characteristics of the 40 schizophrenic investigated were not substantially different than those typically reported (e.g., Seidman, 1982) in the schizophrenia literature; a significant proportion (i.e., 60-75%) showed evidence of neuropsychological impairment and a substantial minority (i.e., 25-40%) did not. Specifically, 25% produced Halstead Impairment Indices within the broad range of normal, 17.5% fell within the borderline impaired range, 12.5% were mildly impaired, 35%, moderately impaired and 10% showed severe neuropsychological deficits. To the extent that neuropsychological impairment reflects underlying brain dysfunction the data are consistent with other neuropsychological (e.g., Silverstein & Zeric, 1985) as well as neuroradiological (e.g., Goetz & van Kammen, 1986), and neurophysiological (e.g., Lohr & Jeste, 1986) studies that demonstrate significant brain pathology in a substantial proportion of schizophrenics.

Hypothesis 1

The results of this investigation do not support the position that neuropsychological impairment is uniquely associated with negative symptoms. Comparisons among schizophrenic subtypes, based on Andreasen and Olsen's (1982) criteria, failed to identify significant differences

between positive- versus negative-symptom schizophrenics on any of several global and/or composite indices of neuropsychological impairment. These indices included the Halstead Impairment Index (based on 7 tests from the Halstead-Reitan Neuropsychological Battery considered optimally sensitive to organic brain dysfunction), a Deterioration Index (based on the difference between estimated premorbid and actual WAIS-R Full Scale I.Q.) and Wechsler Verbal, Performance and Full Scale I.Q. Scores.

Overall, both positive- and negative-symptom schizophrenics showed evidence of mild neuropsychological impairment and intellectual deterioration in the order of 11-12 I.Q. points from estimated levels of premorbid cognitive functioning. These findings suggest that neuropsychological impairment is not an exclusive characteristic of negative-symptom schizophrenia and are in line with other recent neuropsychological studies (Bilder et al., 1985; Green & Walker, 1985; Kaplan et al., 1988) which describe cognitive impairment in association with positive symptoms of schizophrenia. While the patterns of deficits may be qualitatively different in positive- versus negative-symptom schizophrenia, the present study clearly suggests that both subtypes are equally compromised in terms of degree of impairment of general adaptive and problem-solving ability.

The present study also examined the

neuropsychological characteristics of two additional "subtypes" with the understanding that positive and negative symptoms represent distinct, but not mutually exclusive dimensions of pathology (Volkow et al., 1987b). This position is based on the theoretical orientation that positive and negative symptom complexes do not always allow for discrete classification in that many patients show some combination of both or perhaps neither symptom at any one time.

Comparisons among subtypes, including schizophrenics who did not meet criteria for either positive- or negative-schizophrenia or who met criteria for both, suggested a tendency for schizophrenics without prominent symptoms (Neither) to perform better than relatively symptomatic schizophrenics (Positive, Negative, Both) on neuropsychological tasks. In the present study schizophrenics without prominent symptoms generated mean scores higher than other subgroups on 26/29 neuropsychological variables and it was determined that this was not a chance variation. In addition, the mean Halstead Impairment Index of this subgroup (.36), while not significantly lower by statistical criteria, falls within the broad range of normal (i.e., <.51), whereas all other group means would be judged impaired by clinical standards (Reitan & Wolfson, 1985). Thus, these findings suggest that, in general, schizophrenics with proportionately few

symptoms are more likely to perform better on neuropsychological tests than those who have prominent or marked symptomatology independent of the positive-negative distinction. In other words, schizophrenics whose symptoms are well controlled or in remission appear less neuropsychologically impaired than those whose symptoms are more prominent and less well managed. These findings support other recent investigations (e.g., Hansen, Paredes, Koczapski & Kogan, 1987) which report improved neuropsychological functioning in schizophrenics treated with phenothiazines.

In summary, this study does not support the hypothesis that neuropsychological deficits are unique to negative-symptom schizophrenia. The results of level-of-performance comparisons on global indices of neuropsychological impairment indicate that positive and negative-symptom schizophrenics are equally impaired; both subtypes show mild impairment of general adaptive and problem solving ability. Thus, the present findings suggest that cognitive impairment is characteristic of both positive- and negative-symptom schizophrenia although qualitative neuropsychological differences may exist between the two subtypes.

The absence of significant differences in overall level of neuropsychological functioning between positive- and negative-symptom schizophrenics argues against the

position of Crow (1980; Crow et al., 1982; Crow et al., 1986) and Andreasen (1982; Andreasen & Olsen, 1982; Andreasen, 1985a) who exclude cognitive impairment from their definition of positive-symptom schizophrenia. The results of this and other recent neuropsychological investigations (Bilder, 1985; Green & Walker, 1985; Kaplan et al., 1988), which have examined cognitive functioning in a more comprehensive and direct manner, suggest that neuropsychological impairment is generally associated with schizophrenia and neither unique nor more severe in patients whose symptoms are predominantly negative.

Hypothesis 2

While level of performance comparisons between positive- and negative-symptom schizophrenics did not suggest significant differences in degree of overall impairment, the possibility of qualitative differences in neuropsychological functioning was also investigated. Green and Walker (1985) previously reported that positive and negative symptoms may be associated with different performance patterns on neuropsychological tests. Using a brief neuropsychological battery Green and Walker (1985) reported an association between positive symptoms and deficits on tests that involve short-term verbal memory and negative symptoms with poorer performance on tests that measure visual-motor and visual-spatial skills. One

purpose of the present study was to attempt a replication of Green and Walker's findings, using an independent and more comprehensive battery of tests, and to identify patterns of deficit which, if found, may be of lateralizing or localizing significance.

From a lateralizing perspective the Green and Walker (1985) study suggests, but does not explicitly state, that positive symptoms may be associated with greater left hemisphere dysfunction, whereas negative symptoms may implicate greater right hemisphere dysfunction. Goldstein (1986) has also suggested that positive symptoms, especially paranoid thinking, may be associated with left hemisphere dysfunction. More recently, Gruzelier, Seymour, Wilson, Jolley and Hirsch (1988) reported that patients with the "active syndrome" (i.e., positive-symptom schizophrenics) showed more deficits on the Block Span test (right hemisphere), while patients with the "withdrawn syndrome" (i.e., negative-symptom schizophrenics) showed more deficits on the Digit Span test (left hemisphere). Each of these interpretations is based on the understanding that verbal skills tend to be mediated by the left hemisphere and non-verbal, visual-spatial skills by the right hemisphere (Bryden, 1982), at least in the intact brain. In this study the possible association between positive versus negative symptoms and right versus left hemisphere

dysfunction was examined directly.

The results of discriminant function analyses failed to support the hypothesized relationship between symptom presentation and neuropsychological evidence of lateralized cortical dysfunction. While a substantial proportion (approximately 95%) showed evidence of lateralized impairment on such measures as the Tactual Performance Test, no relationship between positive or negative symptoms of schizophrenia and neuropsychological profiles suggesting lateralized impairment could be demonstrated. In fact, no symptom or combination of symptoms adequately discriminated schizophrenics showing lateralized neuropsychological deficit patterns.

The present study did however provide some support for the position (Green & Walker, 1985; Kaplan et al., 1988) that positive and negative symptoms are associated with different patterns of neuropsychological deficit. However, the pattern observed in the present study was only a partial replication of the deficits pattern reported by Green and Walker (1985).

Green and Walker (1985) reported an association between positive symptoms and deficits on tests that involve short-term verbal memory (Busche List Learning Test, Token Test and Sentence Repetition) relative to control subjects. Similarly, Kaplan et al. (1988) also found, among never-medicated schizophrenics, that patients

with positive symptoms had less adequate immediate recall of passages (Logical Memory subtest; Wechsler Memory Scale) and a trend towards a deficit in registration of verbal information. In the present study positive symptoms were likewise associated with poorer performance on tests of verbal learning and memory (Rey Auditory Verbal Learning and Babcock Story Recall, Delayed Recall). Thus, the association between positive symptoms and deficient performance on tests of verbal learning and memory appears to be a replicable finding despite the use of independent neuropsychological measures.

Clinically, deficits in learning and memory are typically associated with underlying temporal lobe dysfunction and deficits in the registration and recall of verbal information in particular, with left temporal lobe impairment (Lezak, 1983). However, the purported relationship between positive symptoms of schizophrenia and underlying left temporal lobe dysfunction remains largely speculative.

Regarding neuropsychological correlates of negative symptoms of schizophrenia, Green and Walker (1985) report an association with poorer performance on tests that measure visual-motor and visual-spatial skill (Purdue Pegboard, WAIS-R Block Design and Benton Visual Retention Test). This finding was not replicated in the present study. Rather, the data suggest a relative deficit in

verbal fluency/productivity (Controlled Word Association Test) as well as impaired Digits Backward performance (Digit Span; WAIS-R). Only to the extent that deficient Digits Backward performance may be the consequence of impaired ability to mentally rotate information in short-term working memory is there even partial support of Green and Walker's (1985) findings. This theory rests on the premise that impaired capacity to reverse digits is related to reduced visual scanning efficiency (see Lezak, 1983, 268-270), however, a general relationship between negative symptoms and visual-motor/visual-spatial deficits was not found.

In the present study, negative symptoms were associated with impaired verbal fluency/productivity. Regretably, non-verbal fluency/productivity was not assessed, therefore it is impossible to state whether the deficit is generally related to decreased productivity (both verbal and non-verbal) or specifically verbal in nature. Including a non-verbal fluency test, such as Design Fluency (Jones-Gotman & Milner, 1977) in the neuropsychological battery may have been useful for evaluating the specialized abilities of anterior parts of the right hemisphere just as tests of verbal fluency tap those of the left frontal lobe. This limitation not withstanding, the deficit pattern observed in the present study suggests a relationship between negative symptoms and

diminished verbal output which is in turn typically associated with left frontal lesions (Lezak, 1983, p. 81). Whether or not right-frontal regions are also implicated remains speculative owing to limitations of the test battery.

While initially a positive symptom/left hemisphere dysfunction, negative symptom/right hemisphere dysfunction hypothesis was proposed (but not supported empirically) based on Green and Walker's (1985) earlier findings, the results of this study appear more conducive to a positive-symptom/posterior, negative-symptom/anterior hypothesis than one based on right/left differences. Specifically, the data appear to suggest that negative symptoms may be associated with impaired anterior (frontal) functioning and positive symptoms to impaired posterior (temporal) functioning. Furthermore, deficits when found appear to generally implicate left- moreso than right-hemisphere structures.

Support for this alternative hypothesis can be drawn from frontal lobe studies (see Damasio, 1979) which report changes in emotional responsivity (i.e., apathy, affective flattening), following anterior brain lesions, which closely resemble negative symptoms of schizophrenia. Also, a relationship between temporal lobe dysfunction and positive symptoms of schizophrenia (i.e., paranoid ideation, delusional thinking and formal thought disorder)

has been proposed (Stoudemire et al., 1983). Thus, other behavioral and neuropsychological data exist to support a hypothesized relationship between negative symptoms and frontal lobe dysfunction as well as one between positive symptoms and temporal lobe dysfunction.

Post-hoc analyses, including discriminant function analysis and independent rating of subject protocols by three experienced neuropsychologists, however failed to lend empirical support to the proposed relationship between anterior versus posterior impairment and positive versus negative symptoms of schizophrenia. Nor were performance differences between positive- and negative-symptom schizophrenics readily accounted for on the basis of other factors (e.g., task complexity) when examined according to similar procedures. Thus the significance of what appear to be qualitative differences in neuropsychological performance in patients with positive versus negative symptoms of schizophrenia and their relation to underlying areas of brain dysfunction, remain speculative.

In summary, the only replicable finding with respect to neuropsychological correlates of positive and negative symptoms was the deficit in verbal learning and memory associated with positive-symptom schizophrenia. Deficits, when found among negative-symptom schizophrenics, appear less reliable although comparatively few studies have examined these relationships to date. Furthermore, the

lateralizing and/or localizing significance, if any, of these deficits remains elusive. It is noteworthy, however, that among neuropsychological studies one deficit not thus far associated with negative-symptom schizophrenia (directing the readers attention to Hypothesis 3), is attentional impairment, particularly since it is often cited (Andreasen & Olsen, 1982) as a defining characteristic.

Hypothesis 3

In a series of recent investigations Walker and associates (Green & Walker, 1986a, 1986b; Walker & Harvey, 1986; Walker, Harvey & Perlman, 1988) have examined attentional correlates of positive- versus negative-symptom schizophrenia. To summarize, their data are contrary to the position (Andreasen, 1982; 1983) that attentional deficits are characteristic of negative- but not positive-symptom schizophrenia. Rather, their data support specific attentional correlates of both positive and negative symptom dimensions. In particular, positive-symptom schizophrenics are said to exhibit deficits in selective attention whereas negative-symptom schizophrenics show decreased speed of information processing. The present study sought to further examine attentional correlates of positive versus negative symptom complexes using a more comprehensive battery of

neuropsychological tests tapping varied dimensions of attention and concentration.

Comparisons between positive- and negative-symptom schizophrenics did not reveal differential impairment on any of eight attention tasks, although relative to schizophrenics without prominent symptoms (Neither), negative-symptom schizophrenics showed poorer performance on attention tasks involving manipulation of verbal information in working memory (Digits Backward) and simple information processing (Trails A/B), whereas positive-symptom schizophrenics had a reduced spatial information span (Block Span). In addition, positive and negative symptoms in combination were associated with a lowered verbal information span (Digits Forward).

In general, these findings stand in contrast to the position of Andreasen (1982; 1983) that attentional impairment per se is uniquely associated with negative-symptom schizophrenia and support the position of Walker and associates (Green & Walker, 1986a; 1986b; Walker & Harvey, 1986) that positive- and negative-symptom schizophrenics show specific attentional correlates. However, these qualitative differences are difficult to compare between this and the Walker et al. series of investigations, partly because of differences in specific attentional tasks and partly because the functional skills underlying performance on the various tasks are poorly

understood. At the root of the problem is the lack of a comprehensive theoretical foundation regarding the nature of attentional processes. Nevertheless, the relationship between negative-symptoms and deficits on timed tests of information processing appears to be a replicable finding as evidenced in greater vulnerability to backward masking (Green & Walker, 1986a; 1986b) and deficient Trailmaking performance in the present study.

The finding of attentional correlates of both positive and negative symptom complexes raises the question of whether the Attention subscale is appropriately included as part of the Schedule for Assessment of Negative Symptoms (SANS)? As available data suggest that impairment of attention is not uniquely associated with negative-symptom schizophrenia, consideration might be given to excluding Attentional Impairment from the SANS on theoretical grounds. Furthermore the nonsignificant correlation between the SANS Attention subscale and the SANS Total Score in this and other studies (e.g., Walker et al., 1988) provide empirical support for the position that attentional impairment ratings detract from the internal consistency of the instrument.

On the other hand, part of the problem may lie in the fact that inter-rater reliability is apt to be low because Attention subscale scores are derived largely on the basis of a highly subjective, nonstandardized rating

system. The results of correlational analyses suggest that, contrary to the findings of Walker et al. (1988), an association between observer ratings of attentional impairment derived from interview and attention ratings obtained in the neuropsychology lab. In the present study it might well have been the case that ratings of attentional impairment based on observations made in interview were heavily influenced by the patient's capacity to sustain attention throughout the duration of the interview as well as on the basis of the backward spelling task. It was not surprising, therefore, to find significant correlations between interviewer ratings and both Digits Backward and CPT (a test of ability to sustained attention) performance. However, Digits Backward but not CPT performance was found to be significantly associated with negative-symptoms, suggesting that the backward spelling task is the more valid index of attentional impairment in negative-symptom schizophrenia.

In summary, the psychometric properties of the Attention subscale remain questionable. Given that attentional impairment is considered one of the global symptoms of negative-symptom schizophrenia according to Andreasen's (Andreasen & Olsen, 1982; Andeasen, 1983) subtyping schema, the lack of demonstrated reliability and validity of the scale suggests that further research in this area is clearly needed in order to establish a more

valid framework for subtyping schizophrenic symptoms.

Hypothesis 4

In general, no significant overall correlation was observed between schizophrenic symptoms and neuropsychological status, nor did the positive versus negative symptom distinction prove to be a useful typography for inferring the presence or absence of neuropsychological impairment. In the present study, correlations between the Halstead Impairment Index and SANS, SAPS, and SANS plus SAPS scores were low and nonsignificant. This outcome was surprising as clinical lore tells us that an abundance of symptoms, particularly in the context of an acute episode, is likely to be accompanied by compromised neuropsychological functioning. In contrast, at least among this chronic sample, patients with the most symptoms were not necessarily the most cognitively compromised and vice versa. Whether this relationship would hold if neuropsychological data from acutely ill schizophrenic patients were included in the analysis, is a question which remains to be explored empirically. Thus, the generalizability of the present findings is limited to chronic ambulatory schizophrenics.

Bilder et al. (1985) has recently suggested that a process independent of the positive/negative distinction may be a more valid predictor of neuropsychological

impairment and that stronger relationships between symptoms and neuropsychological performance might be found if different clusters of symptoms had been identified. The results of this study, however, failed to identify any symptom or symptom combination (based on SANS/SAPS subscales) which, when present or absent, would allow for meaningful prediction of overall neuropsychological status. In fact, age, accounting for less than 10% of the total variance, was a better predictor of neuropsychological status than any of the symptom variables. Present findings indicate therefore, that in general, information regarding symptomatology or their domain (i.e., positive versus negative) does not allow for meaningful prediction of neuropsychological status.

Anecdotally, the lack of association between the subject's psychiatric presentation and neuropsychological status was apparent even without the benefit of formal data analyses. In some instances patients who seem highly disorganized in interview showed surprisingly few neuropsychological deficits, while others who presented well in interview showed marked neuropsychological impairment. In general, it was frequently impossible to distinguish, even with the benefit of information obtained in interview, neuropsychologically impaired from neuropsychologically intact schizophrenics. The implication is that cognitive and psychiatric features

should be evaluated independently, and in clinical practice effort should be made to avoid inferences about cognitive functioning on the basis of psychiatric peculiarity.

Despite the lack of overall correlation between symptom magnitude and neuropsychological performance, present findings suggest that chronic schizophrenics who show prominent symptoms, independent of the positive versus negative symptom distinction, are more likely to be neuropsychologically impaired than those whose symptoms are in remission or adequately controlled by neuroleptic medication. In the present study schizophrenics from the Neither group performed consistently better than subjects from all other subtypes (Positive, Negative, Both) on a wide range of neuropsychological tests and generated a mean Halstead Impairment Index within the broad normal range. These findings suggest that schizophrenics whose symptoms are adequately maintained by pharmacological interventions or otherwise in remission are less likely to be neuropsychologically impaired than patients whose symptoms are less well controlled. This observation is in keeping with studies which demonstrate that cognitive functioning is improved by neuroleptic medication (Hansen et al., 1987) and that negative (Breier et al., 1987) as well as positive (Johnstone et al., 1978) symptoms can be alleviated by psychotropic drugs. While this observation may appear to stand in contrast to the previously stated position that

little correlation exists between degree of neuropsychological impairment and symptom prominence it should be clarified that a basic distinction seems possible between schizophrenics who are largely asymptomatic (who have presumably manifested more prominent symptoms at some point in the past) and schizophrenics who show more marked symptomatology. However, when the full range of schizophrenic symptomatology is taken into consideration the relationship between symptoms and deficits becomes obscurred and irrelevent. Therefore, it is possible to say only that schizophrenics who are ill appear to perform less well on neuropsychological tests than schizophrenics whose symptoms are in remission. This general relationship between symptomatic versus nonsymptomatic and neuropsychological test performance is likely nonspecific to schizophrenia but rather an example of the more general relationship between illness and ability to perform optimally on psychological tests.

The lack of more direct correspondence between neuropsychological status and psychiatric presentation, beyond the mere statement that schizophrenics with prominent symptoms are typically impaired relative to those whose symptoms are not, does not preclude the possibility that specific symptoms (e.g., paranoid ideation) have specific neuropsychological correlates. For example, Goldstein and Halperin (1977) reported that the clinical

literature suggest paranoid- perform better than nonparanoid-schizophrenics on ability tests. Similarly, LaRusso (1978) reported experimental evidence which suggested that paranoid schizophrenics are more perceptive than normal subjects regarding nonverbal facial emotional cues. Green and Walker (1986a) found that ratings of formal thought disorder were positively correlated with distraction scores on a Digit Span task. A relationship between thought disorder and neuropsychological impairment has been proposed in several recent investigations (Silverstein & Arzt, 1985; Braff et al., 1988). In another recent investigation, Moscarelli et al. (1989) found alogia to be the only symptom related to ventricular-brain ratio which, in turn, is often associated with neuropsychological impairment (Golden et al., 1980). These findings, therefore, emphasize the importance of understanding varied symptomatology in terms of the cognitive processes underlying specific schizophrenic phenomena. However, at present these relationships remain largely speculative and poorly understood (George & Neufeld, 1985).

The idea that cognitive and psychiatric status are not as related as previously supposed has been corroborated by others researchers. For example, Kaplan et al. (1988) in a recent neuropsychological study, also observed that the presence of greater overall symptomatology did not increase the likelihood of finding cognitive deficits

within a sample of acutely ill and ambulatory schizophrenic men. Similarly, Cleghorn (1988), in a recent position paper, suggests that neuropsychological test performance is not strongly linked to symptoms and that the spectrum of cognitive (and neurological) impairment cannot be adequately accounted for on the basis of the positive versus negative symptom distinction. Rather, he argues for considering neurological, neuropsychological and symptomatic features as separate dimensions. The results of this study support that approach.

Summary

In summary, the results of this investigation do not support the position of Crow (1980; Crow et al., 1982; Crow, et al., 1986) and Andreasen (1982; Andreasen & Olsen, 1982; Andreasen, 1985a) that cognitive and neuropsychological impairment is associated with negative- but not positive-symptom schizophrenia. The hypothesis that neuropsychological impairment is a unique and defining characteristic of negative-symptom schizophrenia was rejected (Hypothesis 1) in view of findings which suggest that positive-symptom schizophrenics are equally impaired according to several global and composite indices of cognitive and neuropsychological impairment.

The position (Green & Walker, 1985) that positive and negative symptoms of schizophrenia are associated with

unique patterns of cognitive functioning was supported in this study. In particular, the association between positive symptoms and deficits in the learning and retention of verbal information appears to be a replicable finding. In contrast, neuropsychological correlates of negative symptoms of schizophrenia appear less consistent from study to study. In the present study negative symptoms were associated with decreased verbal fluency/productivity, while Green and Walker (1985) reported relative deficits on visual-spatial tasks. While several efforts were made to relate, on theoretical grounds, specific symptoms to specific regions of brain dysfunction, no lateralizing or localizing significance could be attached to the various deficit patterns identified in either study. Thus, the hypothesis that deficit patterns unique to positive- or negative-symptom schizophrenia have localizing or lateralizing significance was rejected (Hypothesis 2). Nevertheless the finding that separate types of deficits are associated with different types of symptoms argues for the fundamental validity of the positive versus negative symptom distinction.

This study also supports the position of Walker and associates (Green & Walker, 1986a; 1986b; Walker et al., 1988) that positive and negative symptoms are associated with qualitatively different types of attention deficit contrary to Andreasen (Andreasen, 1982; 1983) who holds

that attention deficits are unique to negative- but not positive-symptom schizophrenia. In the present study, positive symptoms were associated with a reduced spatial information span; a finding which runs contrary to the hypothesis that attention deficits are a unique and defining characteristic of negative-symptom schizophrenia (Hypothesis 3). This finding also detracts from the validity of the Attention subscale of the SANS, although the validity of the backward spelling item from the Attention subscale is supported by neuropsychological findings which suggest that negative-symptoms may be associated with an attention deficit which manifests on tasks that involve the manipulation of verbal information in working memory.

Finally, this study served to demonstrate that the neuropsychological characteristics of schizophrenic patients may not be as closely related to their symptom presentation as previously supposed. While neuropsychological correlates of positive and negative symptom complexes were identified the positive versus negative symptom distinction, or any other symptom combination, does not allow for neaningful prediction of overall neuropsychological status (Hypothesis 4). In fact, the known heterogeneity of memory, cognitive and attentional deficits reported among schizophrenics (Seidman, 1982), coupled with evidence from this and other

recent studies (Kaplan et al., 1988; Cleghorn, 1988) which recognize the dissociation between overall symptomatology and degree of neuropsychological deficit, underscores the need for independent assessment of neuropsychological functioning in each individual case.

Methodological Issues

One obvious limitation of the present methodology was that medication effects were largely ignored in that no attempt was made to match subjects on the basis of type or amount of medication received. Therefore, differences between present results and other neuropsychological investigations may be at least partially attributable to differences in neuroleptic dosage between schizophrenic samples as well as between individual subtypes. Although the type and amount of medication was uncontrolled in this study, Green and Walker (1985) matched their subjects according to amount of medication received (expressed in chlorpromizine equivalents), and Kaplan et al. (1988) reported findings among never- or remotely-medicated schizophrenics. Understanding the effects of medications typically used in the management of schizophrenia is important because these drugs alter neuropsychological performance and symptom presentation, ultimately affecting patient scores and patient classification.

In particular, it is important to note that

phenothiazines (e.g., chloropromazine) exert prominent effects on the basal ganglia and limbic system producing a Parkinsonian-like syndrome which includes psychomotor slowing, indifference to sensory stimuli and reduction of initiative (Julien, 1978). Furthermore, recent studies (Taylor, Saint-Cyr & Lang, 1987; 1988) have shown that cognitive changes in Parkinson's Disease (PD) include a deficit in strategic planning under novel conditions as well as general impairment of executive functions. Thus it is possible that impaired performance on "executive" tasks, when found, may be at least partially attributable to the effects of neuroleptic medication rather than the disease process underlying schizophrenia.

On the other hand a recent review (Hansen et al., 1987) of the effects of phenothiazines on cognitive functioning in schizophrenia suggests that neuroleptics may facilitate more than impair performance on cognitive tests. Flor-Henry and Yeudall (1979) also observed that drug therapy and symptom amelioration led to an improvement in neuropsychological scores which did not appreciably alter the pattern of neuropsychological dysfunction present. Similarly, Walker et al. (1988) reported that controlling for medication dose did not alter the pattern of intercorrelations among symptoms for schizophrenics. In general, medication effects would appear to influence level more than pattern of neuropsychological performance.

A second methodological issue raised within the context of this investigation concerns the criteria for subgroup classification. According to Andreasen's criteria (see Table 1, p. 66), subjects are considered positive-symptom schizophrenics if they show symptom ratings of 4 or more on at least one of four SAPS subscales, or as negative-symptom schizophrenics if they show symptom ratings of 4 or more on at least two of five SANS subscales. Using her criteria, several anomalies of classification occurred.

One anomaly in group classification occurred when schizophrenic subjects failed to meet inclusion criteria because their symptoms were mild but broad-spectrum rather than severe. For example, subject #8 (see Appendix D) showed evidence of symptomatology on all but one of nine SANS/SAPS subcales, yet, despite her abundance of symptoms failed to meet criteria for inclusion in either positive or negative symptom groups. Nevertheless, her SAPS Total of 40 was higher than 60 percent of patients classified as Positive (i.e., SAPS = 14, 14, 24, 28, 32, 36, [40], 48, 52, 53, 59) using Andreasen's cut-off criteria. In contrast, subjects #22 and #34 were classified as Positive on the basis of a single elevated symptom rating and a SAPS Total scores of 14; the same rating obtained by one Negative schizophrenic (#6), and equal to or lower than ratings obtained by two Neither schizophrenics (#8, #12).

These apparent inconsistencies and contradictions raise concerns about the validity of Andreasen's seemingly arbitrary criteria for subtyping.

Meltzer and Locascio (1987) noted similar classification problems in their critique of a 1987 study by Volkow et al. (1987) who used a median split of symptom ratings as opposed to the cutting method of Andreasen. However, similar problems in classification emerged in subtyping a sample of 18 chronic schizophrenics. For example, two patients with equal scores of 3 for positive and negative symptoms were categorized as positive-symptom schizophrenics, two patients with equal positive and negative scores of 4 were classified as negative-symptom schizophrenics, and two patients with higher negative than positive scores were labelled positive-symptom schizophrenics. Furthermore, two negative-symptom schizophrenics reportedly had positive symptoms scores higher than 7/8 patients with positive symptoms. Thus, what appear to be classification anomalies found in this and other investigations underscore the need for empirical evidence to justify continued categorization of schizophrenia into positive and negative subtypes, particularly on the basis of seemingly arbitrary inclusion and exclusion criteria.

In the present study subtypes comparisons were made using both Andreasen's criteria and a median split of

SANS/SAPS ratings. The latter approach resulted in a reclassification of 15% of the 40 subjects, and many differences in neuropsychological performance between subtypes were attenuated by the reclassification. The basis for classification is said to have a significant effect on outcome, so that classification rules should be based on empirically-derived rather than arbitrary cut-off criteria.

A related issue concerns the composition of individual items that make up the symptom rating scales. For example, the questionable validity items on the Attention subscale of the SANS was raised in the context of this investigation. Andreasen (1982) includes "inappropriate affect" on the Affective Flattening subscale of the SANS (with later acknowledged misgivings), however Crow (1980) regards this as a positive symptom. While Crow (1980) and Andreasen (1982) agree that symptoms of Positive Formal Thought Disorder should include "derailment" and "incoherence", Lewine et al., (1983) considers them negative symptoms. Thus some controversy exists as to whether certain behaviors reflect positive or negative symptomatology.

In an effort to provide a more specific rationale for assessing negative symptoms, Carpenter et al. (1988) have proposed a distinction between deficit and non-deficit forms of schizophrenia. They classified 103 psychiatric

outpatients meeting DSM III and RDC criteria for schizophrenia or schizo-affective disorder based on the continued presence of negative symptoms over time (deficit schizophrenia) versus secondary and/or episodic negative symptoms that may occur in patients acutely psychotic or depressed (non-deficit). The criteria for negative symptoms differs from those of Andreasen and Olsen (1982) in that the focus is on "direct" rather than "derivative" symptoms. For example, loss of social drive is considered a direct negative symptom, whereas social withdrawal is the complex and derivative outcome of a range of schizophrenic symptoms, either positive or negative, interacting with the individual's specific interpersonal and cultural environment. Thus social withdrawal due to paranoid perception would not be considered a negative symptom. These and other efforts (e.g., Kay, Flazbein & Opler, 1987) to develop more specific rationales and more standardized instruments with demonstrated reliability and validity do much to enhance the quality of research in this field.

The third methodological issue concerns the fundamental validity of the positive versus negative symptom distinction. While much of the recent appeal of this distinction lies in the fact that it unites our current understanding of phenomenology, pharmacology, pathophysiology and neuropsychology of schizophrenia into a single comprehensive hypothesis, researchers have now begun

to evaluate the positive-negative dichotomy more critically to determine whether an empirical basis for classification exists. Meltzer and Locascio (1987), for example, re-analyzed data from Volkow et al. (1987), subjecting it to formal cluster analysis, and failed to find evidence of discrete subtypes of schizophrenia on the basis of positive versus negative symptomatology. In general, Meltzer and Locascio (1987) were unable to find any strong empirical evidence of subtypes of schizophrenia based on either continuous or discrete symptom variables in univariate or multivariate distributions.

The lack of statistical independence of positive and negative symptoms has also been cited as justification for dismissing the positive versus negative symptom distinction on grounds that the symptom clusters co-exist and do not constitute a discrete basis for classification. Alternatively, the lack of statistical independence of positive and negative symptoms may be interpreted as evidence that positive and negative symptoms represent distinct, but not mutually exclusive dimensions of psychopathology with perhaps independent biological and neuropsychological correlates. The results of this study identified some and replicated other specific cognitive and attentional correlates in relation to positive versus negative symptoms of schizophrenia. This study therefore supports the fundamental validity of the positive versus

negative symptom distinction, but at the same time recognizes that this distinction does not allow for meaningful prediction of individual patterns of neuropsychological functioning. This research also recognizes that positive and negative symptoms do not provide a mutually exclusive basis for discrete classification and that many patients show some combination of symptoms at the same time and to varying degrees by examining neuropsychological correlates of schizophrenic subjects with both positive and negative symptoms. Accordingly, many researchers (e.g. Green & Walker, 1985) have now adopted the view that symptoms should be conceptualized (and for statistical purposes, analyzed) as continuous rather than discrete variables. This model would appear to be more in keeping with current understanding of the relationship between the symptom complexes.

Finally, one cautionary note pertaining to the statistical analyses in the present study. In exploring the possibility that neuropsychological variables discriminate positive- from negative-symptom schizophrenics multiple ANOVA's were performed on an extensive number of neuropsychological tests. Accordingly, the large number of dependent variables combined with the fact that neuropsychological test scores tend to be highly intercorrelated, suggest that multivariate analyses (e.g.,

MANOVA/MANCOVA) would have been more appropriate than conducting a series of univariate (e.g., ANOVA/ANCOVA) tests. The latter approach also generally raises concerns over the possibility of spurious, positive findings. However, given the overall negative results the potential for chance-inflated findings does not appear to have been a critical issue in this instance.

On the other hand, there were several instances in which differences appeared clinically important but did not reach statistical significance. This may have been due to either an insufficiently large sample size and/or, in certain instances, the use of extremely conservative tests (e.g., Scheffe) as the basis for means comparisons. Nevertheless, various trends, where identified, were generally similar to the pattern of deficits identified by investigators (e.g., Green & Walker, 1985) who subjected their data to the scrutiny of multivariate statistics. The findings were particularly consistent with regard to the association between deficits in verbal learning/memory and positive symptoms of schizophrenia. Thus, current findings to not appear to be an artifact of the statistical procedures employed.

In conclusion, the results of this and other recent neuropsychological investigations have served to identify specific cognitive and attentional correlates of positive- and negative-symptom schizophrenia. More importantly, they

demonstrate that differential deficits in relation to specific symptom clusters do not necessarily constitute a discrete or readily defined basis for classification as many patients show evidence of both positive and negative symptomatology (Tandon & Greden, 1989). In essence, the notion of distinct "subtypes" appears misleading as the two "syndromes" may be less dichotomous than previously assumed. In fact, other assumptions about the symptom complexes and their clinical features are also being modified in non-neuropsychological investigations. For example, Johnstone et al. (1986) examined the relative stability of positive and negative symptoms and found, contrary to popular notion, that negative symptoms are not as intractable as previously supposed, while Breier et al. (1987) have found that positive and negative symptoms demonstrated similar patterns of reduction and exacerbation during neuroleptic treatment and withdrawal. In sum, the positive versus negative symptom distinction, while retaining its fundamental validity, appears to be undergoing considerable revision since it was first introduced by Crow (1980) and Andreasen (1982) nearly a decade ago.

STUDY 2
COGNITIVE REMEDIATION IN SCHIZOPHRENIA: A NEUROPSYCHOLOGICAL MODEL

In the preceding study the neuropsychological correlates of positive versus negative symptoms of schizophrenia were examined. Theoretical notions aside, the identification of neuropsychological impairment in schizophrenic patients is important because of the implications for patient management. It is important, for example, to assess each patient's cognitive limitations and deficits in order that appropriate decisions are made regarding treatment and rehabilitation; in certain cases a patient's poor prognosis may be directly related to underlying neuropsychological impairment (Acker, 1986; Prigatano et al., 1986; Prigatano, 1987). In such cases neuropsychological rehabilitation strategies may be a viable treatment alternative to traditional psychiatric interventions (e.g., group therapy, individual therapy) especially since it is widely recognized that traditional forms of psychiatric treatment for persons with schizophrenia have led to very poor outcomes (Ryan, Bell & Metcalf, 1982). In fact, Anthony, Bueel, Sharratt and Althoff (1972) reported the recividism base rate for psychiatric inpatient treatment programs as 30-40% at 6 months, 40-50% at 1 year, and 65-75% at 3 to 5 years.

The following section contains a review of an emerging rehabilitative perspective with potential for the remediation of attention, memory, cognitive and behavioral deficits which handicap a significant proportion of schizophrenic patients. Thereafter, the results of a preliminary attempt at computer-based cognitive remediation in a sample of four chronic outpatient schizophrenics will be presented.

Cognitive Remediation

Cognitive remediation, or cognitive rehabilitation, consists of numerous intervention strategies designed to ameliorate the neurobehavioral consequences of brain injury (Goldstein, 1986). This process can be either compensatory (i.e., learning to use preserved abilities to compensate for those skills no longer available) or restitutive (i.e., relearning skills lost through injury). The approach is based on the concept that cognitive remediation is essentially a learning (or relearning) paradigm to be used in conjunction with the treatment of illness or disease. Within the context of the current investigation "cognitive" is broadly defined as pertaining to the encoding, transformation, storage, and use of information for the purpose of regulating behavior (George & Neufield, 1985); and "remediation" is the processes and procedures which provide patients with the behavioral repetiore needed to

solve problems or to perform tasks that seem difficult or impossible (Diller & Gordon, 1981). From a rehabilitative perspective Sohlberg and Mateer (1989) refer to cognitive remediation as the therapeutic process of increasing or improving a patient's capacity to process and use incoming information so as to facilitate increased functioning in everyday life. For neuropsychologists, cognitive remediation represents a relatively new field of contribution beyond their traditional role of assessment. As a field of specialization cognitive rehabilitation is still very much in the "tool-building" stage (Trexler, 1982; Prigatano et al., 1984; Finlayson, 1985).

The rehabilitation effort is generally a multidisciplinary one. Speech pathologists are trained to remediate language difficulties, physiotherapists are concerned with restoration of motor function and occupational therapists focus on the development of general and practical skills. The unique contribution of neuropsychology is said to be in the identification of higher level cognitive deficits (i.e., abstraction, logical analysis and reasoning) and to use this information in the development of programs for their remediation (Reitan & Wolfson, 1985; Cicerone & Tupper, 1986; Sohlberg & Mateer 1989). This approach addresses the need for general retraining of higher-level cognitive functions, particularly reasoning, problem-solving and

conceptualization, in an attempt to restore a meaningful quality of life and to prepare the individual to deal with the problems of everyday living.

The goal of cognitive remediation is the treatment of cognitive deficits to improve quality of life (however broadly defined), facilitate psychosocial adjustment and, when appropriate, facilitate return to gainful employment.

Cognitive Remediation of Neurological Disorder

Many models for cognitive remediation in brain-based disorders are available (Diller, 1976; Reitan, 1979; Diller & Gordon, 1981; Caplan, 1982; Trexler, 1982; Ben-Yishay, 1983; Bracy, 1986; Christensen, 1986; Gross & Schutz, 1986; Alfano & Finlayson, 1987; Szekeres, Ylvisaker & Cohen, 1987; Trexler, 1987; Sohlberg & Mateer, 1989), and cognitive remediation techniques, in their various forms, have been applied to a variety of neurological conditions. Among the types of disorders for which cognitive remediation programs have been developed are closed head injury (Prigatano, Fordyce, Zeiner et al., 1984; Scherzer, 1986), stroke (Carmon, Gordon, Bental et al., 1977), alcoholism (Binder et al., 1980), cerebral palsy (Leftoff, 1979) and spina bifida (Gluckman et al., 1980). On the other hand, while progressive brain diseases such as multiple sclerosis and Alzheimer's Disease are increasingly debilitating, remediation of deficits in disorders

involving static brain lesion has generally attracted more clinical and research attention.

Fundamental to most models of cognitive remediation is the recognition of some form of recovery mechanism (Finger, 1978; Bach-y-Rita, 1980; Miller, 1984; Uzzell, 1986; Finger, 1989). According to Sohlberg and Mateer (1989) the most commonly cited central nervous system mechanisms of recovery include (a) diaschisis, a process involving the reestablishment of unimpaired neurologic systems temporarily compromised due to acute factors such as edema and increased intracranial pressure, (b) axonal growth, involving regeneration of neural elements in cells not completely destroyed by brain insult, (c) denervation sensitivity, by which post-synaptic receptors, typically in the peripheral nervous system, become more sensitive to neurotransmitter agents and, (d) substitution, a mechanism whereby existing intact brain structures assume functions previously held by lesioned areas.

Based on a survey of rehabilitation centres throughout North America offering cognitive remediation therapy, Sohlberg and Mateer (1989) suggest that most programs adhere to one of three basic approaches. One approach (General Stimulation Approach) uses tasks that encourage cognitive processing at any level with the assumption that any stimulation will translate into improved mental functioning. Another approach (Functional

Adaptation Approach) assumes that cognitive function cannot be improved with specific retraining, but is best carried out in a wholly functional environment (i.e., living area and workplace). The third approach (Process-Specific Approach) is toward targeted remediation of specific cognitive areas through direct retraining. This latter approach also teaches individuals ways to use intact abilities to compensate for those lost through injury or insult. It is in the facilitation of this process that rehabilitation psychologists are most likely to make a direct contribution (Alfano & Finlayson, 1987; Sohlberg & Mateer, 1989). The essential strategy of this approach is repeated administration and monitoring or performance on hierarchically organized treatment tasks and, when set criterion levels are achieved, a more challenging component of the targeted skill is introduced.

Much of the early work of rehabilitation psychologists was directed toward the acquisition of specific skills or the extinction of undesirable behavior with relatively little attention having been devoted to the training of brain functions in general and reasoning ability in particular (Finlayson, 1985). For example, behavior modifiers, very actively involved in the rehabilitation effort, design programs which are directed at highly specific target behaviors (i.e., such as the use of shaping by reinforcement and suggestion to improve

typing and handwriting performance in a hemiplegic). Even though the modification of specific problem behaviors is of definite value, the overall quality of life is probably better represented by higher level brain functions (Reitan, 1979). Ironically, there has been a great tendency in rehabilitation to focus on the obvious deficits and provide training in specific skill areas with relatively little attention having been paid to the cognitive abilities which subserve or mediate these skills. Thus, the identification of these higher level deficits, and the development of programs for their remediation, represents a new and important challenge in the areas of neuropsychology and rehabilitation (Reitan, 1979; Reitan & Wolfson, 1985).

Reitan (1979) and Reitan and Wolfson (1985) have repeatedly emphasized the need for general retraining of higher level brain functions with the goal of providing the brain damaged individual with the core cognitive abilities to deal effectively with all aspects of daily living. He describes three major areas of neuropsychological deficit based on current conceptions of brain-behavior relationships. These involve: 1) language functions (both expressive and receptive), 2) abilities in the area of visual-spatial as well as temporal/sequential relationships (both receptive and expressive), and 3) the ability to engage in general adaptive and problem-solving behavior (based on both receptive and expressive functions). It is

the latter of these abilities which has traditionally received the least amount of attention. Whereas the field of physical medicine (physiatry) has focused on the assessment of sensory and motor deficits, Reitan (1979) argues that it is the higher level aspects of impaired brain functions which may be of critical importance in the quality of life achieved by the brain damaged individual.

The development of general thinking skills is not only directly related to quality of life but is thought to have a critical impact on the individual's ability to utilize and exploit many of the rehabilitation efforts described here (Finlayson, 1985). With the understanding that brain dysfunction gives rise to both general and specific deficits, Reitan (1979) devised a rehabilitation program which addresses the need to stimulate a wide range of core cognitive and general adaptive abilities. The program, entitled "Reitan Evaluation of Hemispheric Abilities and Brain Improvement Training (REHABIT)" emphasizes the critical importance of reasoning and abstraction skills in recovery from brain-damage. REHABIT provides training in 5 general areas of neuropsychological deficit. Other researchers have developed programs which provide specific training in the areas of attention (e.g., Ben-Yishay & Gordon, 1978; Sohlberg & Mateer, 1987; Ponsford & Kinsella, 1988; Sohlberg & Mateer; 1989), orientation (e.g., Sohlberg & Mateer, 1989), memory (e.g.,

Schacter, Rich & Stampp, 1985; Glisky, Schacter & Tulving, 1986), and general executive functions (e.g., Sohlberg & Mateer, 1989).

Most cognitive rehabilitation models stress the importance of comprehensive neuropsychological evaluation prior to planning a remediation program (e.g., Reitan & Wolfson, 1985; Sohlberg & Mateer, 1989). Clearly, the nature of the person's deficit must be recognized and described before any meaningful rehabilitation efforts can be undertaken. Reitan, in particular, advocates the position that the neuropsychological measures be used not only for diagnostic purposes, but that the same tests be used (or variations of them) as training procedures; reasoning that measures from the HRB, which tap a broad range of brain functions, are an equally effective tool for stimulating a broad range of brain functions. While this approach makes intuitive sense, it does pose methodological problems in regard to evaluating the overall effectiveness of cognitive remediation efforts when the same test instruments (or alternate forms) are used to reassess the patient's neuropsychological status as in the pre-post experimental design. Using this approach, significant improvement in performance may be observed, but the generalizability of these findings is severely limited. An argument can be made for using assessment procedures which are unrelated to training techniques in ways other

than the skill areas they tap.

The impact of cognitive remediation techniques has traditionally been examined in two general ways. One design assigns samples of similarly impaired patients randomly to two groups. One group receives cognitive retraining while the other does not. Pre- and post-test performances of each group on a battery of neuropsychological tests are compared in hopes of demonstrating differential improvement for patients with special input (e.g., Prigatano et al., 1984). The second approach follows the single case experimental design to demonstrate the efficacy of a given intervention (e.g., Gianutsos, et al., 1979; Finlayson, et al., 1984).

Studies lending empirical support to the effectiveness of cognitive remediation programs are now beginning to appear in the clinical literature in increasing numbers (e.g., Sohlberg & Mateer, 1987). These studies are encouraging because they demonstrate modest but statistically reliable improvement on standardized neuropsychological tests while other data indicate that neuropsychological measures are good predictors of ability to carry out activities of daily living and performance of basic social roles.

A number of investigators have concerned themselves with neuropsychological test scores as predictors of rehabilitation potential as well as predictors of

functioning in the everyday world. For example, McSweeny et al. (1985) found that complex tasks such as the Trails B from the HRB, which taps, among other skills, cognitive flexibility, sustained vigilance and perceptual-motor speed, serve as excellent predictors of quality of life. Prigatano et al. (1984) found the Wechsler Digit Symbol to be a powerful discriminator between closed head injury patients who return to work and those who do not. They found that if the patient was performing at or above the lower limit of the normal range by the end of rehabilitation that he/she has the basic cognitive capacities to be taught work skills and to be competitive in terms of efficiency of functioning, at least for some jobs. Still, greater understanding of the extent to which improvement in neuropsychological status generalizes to extra-test situations and the extent to which improvement is manifest, not only in terms of altered test scores but in observable aspects of everyday living, is needed. It may be the case, for example, that improved neuropsychological status does not directly or immediately result in better psychosocial adjustment, but rather provides the necessary foundation for the subsequent development of more practical and marketable skills which only then translate into sustained independent living and productivity.

The personality and neuropsychological

characteristics of patients who appear to benefit from cognitive remediation procedures are also being explored. Much of the impetus for this work stems from a desire to recognize rehabilitation potential on the basis of objective criteria. Prigatano et al. (1984) were surprised to find that some patients, who intuitively appeared to be ideal candidates for their Neuropsychological Rehabilitation Program (NRP) failed, while others, who looked as if they were going to be poor candidates, succeeded. Preliminary findings suggest that those individuals who are aware of their deficits and who show a willingness to use compensatory strategies to work around their deficits make the best candidates (Prigatano et al., 1984) Patients who seemed to benefit most on the NRP were characterized by Average Impairment Ratings no greater than 2 to 2.25 (moderate impairment), a Digit Symbol subtest pretraining score of at least 6 (lower limit of the average range), Paired Associate Learning subtest of the Wechsler Memory Scale approaching normal limits, and Performance I.Q. at least in the 80's. In contrast, pre-existing characterological or personality disturbances, which affect motivation, appear to foster poor outcome (Prigatano et al., 1984).

While cognitive remediation techniques bring some optimism to the problems of brain-damaged patients, in actual clinical practice it is generally felt that a great

deal of time and effort is required for relatively small gains (Finlayson, 1985). In addition, most cognitive remediation procedures are redundant and labour-intensive, making it difficult for the clinician to repeatedly muster the necessary enthusiasm. Finlayson (1985) points out that the advent of inexpensive personal microcomputers has led to an interest in using the computer as the vehicle for cognitive remediation (e.g., Kurlychek & Glang, 1984; Sunday, 1985; Dorval & Pepin, 1986; Glisky et al., 1986; Finlayson et al., 1987). Not only can microcomputers perform repetitive tasks without error and boredom, tasks can often be programmed into game form to make them more attractive to the patient.

Lynch (1983) was among the first to draw attention to the idea of using computer games for cognitive remediation. The features which have made computer games immensely popular in recent years are the same ones which are likely to make them attractive to the brain injured patient. The popularity of computer games can be attributed to several factors. First, they are enjoyable; high-resolution graphics and dramatic sound effects make them attractive and reinforcing for the player. A second reason is their flexibility. Most computer games offer the player different difficulty levels which keeps the task challenging. If carefully programmed, computer-based training procedures can be adapted to the individual's

needs by matching increments in level of difficulty with his or her rate of progress. In addition, computer games are often programmed with random obstacles which serve to make the game novel and unpredictable. Finlayson, Alfano and Sullivan (1985) indicate that novelty, surprise and increasing difficulty are three intrinsically motivating features of microcomputer games which can be manipulated in rehabilitation settings to satisfy intellectual or cognitive curiousity. A third reason is their accessibility. Since many games are housed in a compact cartridge they can be easily transported between the rehabilitation centre and home. Pocket-sized electronic games also allow someone to play during trips on the bus or while waiting in the doctor's office. The fact that microcomputers are fairly inexpensive has also contributed to their popularity. Small, self-contained electronic games can be purchased for as little as $20.00 although games which require a small microcomputer are relatively more expensive. A Commodore 64 Computer, for example retails for under $1000.00, including keyboard, disk drive and monitor. Separate game cartridges are likely to cost between $10.00 and $50.00 depending on the sophistication of the software. A fifth reason for their popularity is that playing video games can be educational and/or therapeutic. The playing of electronic games is an active and interactive process in contrast to many learning

paradigms which are passive and receptive. Computer games also provide immediate and varied feedback which can be presented in a number of exciting, graphic and colorful ways and immediacy of feedback is known to be a critical variable in the learning process.

Given their capacity for data storage, microcomputers can also be used to record progress across trials. The advantage is that patient data is permanently stored for both program monitoring and possible data analysis.

In recognition of the many potential advantages of computer-based delivery of cognitive remediation programs (Gianutsos, 1980; Lynch, 1982; Miller, 1984; Finlayson, 1985) microcomputer applications are gaining in popularity. Dorval and Pepin (1986) recently used a microprocessor to test the hypothesis that spatial visualization test scores could be improved by video-game playing. After only eight sessions (each session consisted of 5 plays) subjects who played the Zaxxon game (Colecovision) showed significant improvement in their spatial visualization skill relative to controls, as measured by the Space Relations Test of the Differential Aptitude Tests. Their results suggest that spatial visualization is a trainable skill and that scores on tests that tap spatial visualization can be improved by video game playing. Their subjects were, however, undergraduates and not brain injured patients. Thus the

ability of neurologically impaired persons to benefit from this type of intervention is questionable.

Finlayson et al. (1987) used microcomputer assisted procedures to remediate attentional and perceptual-motor deficits in a 36 year old woman with a right temporal-parietal lesion and a dense left hemiplegia. The cognitive retraining program, based on the REHABIT model, consisted of 12 consecutive, weekly hour long sessions on the microcomputer. Take-home exercises were also given every other week. Pre- and post-treatment comparisons of her performance on the HRB revealed measurable improvement on most tests, particularly those tapping new learning and general problem-solving ability, although her performance on measures of sustained attention and concentration still reflected mild residual impairment. Although based on a single case study, their results are encouraging with respect to the potential efficacy of microcomputer assisted cognitive remediation procedures in some cases of adult brain damage.

At present the number of empirical studies validating the use of computer-based cognitive remediation programs remains relatively small. In fact, Finlayson (1985) notes that a definitive study of the efficacy of cognitive remediation in the general sense is still lacking. However, these types of studies now appear in increasing numbers (e.g., Glisky et al., 1986; Gray &

Robertson, 1988; Robertson & Gray, 1988).

While the use of cognitive remediation techniques to remediate deficits associated with neurological disorder represents the majority of work in the field, the application of these techniques to the cognitive problems of mental illness has been the subject of recent speculation (Erikson & Binder, 1986). Unfortunately that speculation has not yet been translated into programs to remediate such impairments. Some seminal work is however now being conducted in that area (Anthony & Farkas, 1982; Yozawitz, 1986).

Cognitive Remediation of Neuropsychiatric Disorder

Although the vast majority of work in the field of cognitive remediation is directed toward neuropsychological deficits associated with acquired brain dysfunction, there is emerging opinion that some psychiatric patients whose deficits may also be brain-based, may potentially benefit from cognitive remediation (Erikson & Binder, 1986). In principle, cognitive remediation efforts with psychiatric patients is similar to working with neurologically inpaired patients in that the treatment goal is the same: to maximize independent functioning among persons whose functional deficits limit reasonable psychosocial adjustment.

Diamant (1978) was among the first to attempt

cognitive remediation procedures with psychiatric patients. Diamont provided "neuropsychological therapy" to 11 psychiatric patients with medical evidence of brain damage with the aim of improving the functioning of the brain by means of psychological techniques. Neuropsychological therapy consisted of training in the areas of concentration, memory, psychomotor speed, psychomotor co-ordination, space orientation and cognitive flexibility. Training materials and pre/post-evaluation procedures consisted of, for each psychological function, separate tests tapping similar abilities. The training program was carried out over a period of eight to twelve weeks based on one to two sessions per week. Although statistical analyses of patient performance was not undertaken, Diamant noted that one patient showed "hardly any" improvement in the trained psychological functions, three showed only "a little" improvement, five substantial improvement and two "sharp" improvement. His results, despite nonstatistical analyses of data and the small portion of patients showing significant improvement relative to the total group suggest that systematic training of disturbed psychological function for psychiatric patients with brain-based deficits may be a helpful therapeutic tool in some instances.

Yozawitz (1985) also applied cognitive remediation techniques to a general psychiatric population. He developed an individualized cognitive "habilitation"

program for 6 general psychiatric patients (4 schizophrenic and 2 affective disorder) for whom cognitive deficits were an obstacle to long-term treatment success. The conceptual basis for cognitive habilitation training was that behavioral strengths subserving adaptive functioning can be used to improve cognitive, perceptual and motor abilities with focused and repeated practice. Accordingly, patients received training for conceptual, language, visual-spatial and motoric disability. One-to-one training was provided based on 12-16 hours per month over a period of 10-23 months. Post-treatment evaluation showed significant improvement on several neuropsychological measures, however the clinical significance of these changes with respect to the social, educational and vocational adaptive functioning of the patient within the community was not assessed. It was however, of theoretical significance that the pattern of post-treatment improvement following cognitive habilitation was similar to that observed in nonpsychiatric (i.e., closed head injury) controls. Although the nature of the similarity was, unfortunately, not described the observation suggests that some psychiatric patients resemble closed head injury patients in their ability to benefit from cognitive remediation and that their acquired cognitive deficits are not necessarily fixed.

The two cognitive remediation programs outlined above seem to support at least tentatively the hypothesis

that psychiatric patients with neuropsychological deficits may benefit from cognitive remediation in a manner similar to patients with identifiable neurological disease. Taken in the context of data (Crow, 1980) which indicate substantial neuropsychological impairment in at least one subtype of schizophrenia, make this population a logical target for cognitive remediation therapy. Furthermore, additional data (Andreasen, 1982) which suggest the combination of negative symptoms and neuropsychological deficits translate into poor prognoses (Andreasen, 1982) make cognitive remediation a logical adjunct to traditional psychotherapy.

In summary, the position is taken that while there is much speculation about the etiology and pathophysiology underlying positive and negative symptoms, the most important aspect of their study in schizophrenia is ultimately that of treatment. The literature reviewed has suggested that negative-symptom schizophrenics generally do not respond to neuroleptic medication. Since antipsychotic medication is the hallmark of successful management of schizophrenic symptoms, this failure to benefit from neuroleptics constitutes a significant treatment problem. Clinical importance aside, the chronic course and poor prognosis associated with negative symptoms presents a bleak outlook for those schizophrenics who present in this fashion (Levine, 1985). The question of cognitive

remediation in schizophrenia, as a rehabilitative model therefore seems directed principally toward the management of those negative-symptom schizophrenics whose poor prognosis can be directly or indirectly attributed to neuropsychological deficit.

Yozawitz (1985) and other proponents of cognitive remediation therapy suggest that to the extent poor premorbid cognitive states contribute to a patient's chronic presentation, strategies that can treat these cognitive limitations by increasing resourcefulness and coping ability should be of prognostic and of therapeutic importance. Certainly cognitive disability is critical to the issue of social and vocational adjustment for psychiatric patients. Therefore programs which focus on the training of fundamental cognitive and perceptual skills are actively being developed. The possible role of cognitive remediation as a useful adjunct to traditional psychotherapy in improving quality of life for some schizophrenic patients will be explored in a small sample (n=4) of schizophrenics.

Hypothesis

Cognitive remediation with computer assistance has been found useful in rehabilitating some types of brain damaged patients. The application of cognitive remediation techniques in schizophrenia, now recognized as a brain

based disorder, is directed, fundamentally, toward the potential for management of those schizophrenics whose poor prognosis is directly or indirectly attributed to intellectual impairment and neuropsychological deficit.

The present study explores the potential applicability of a computer-based cognitive remediation program to four schizophrenic patients. This pilot investigation is based on the premise that schizophrenia is amenable to the same interventions as other brain based disorders. The hypothesis that cognitive remediation may improve quality of life for some schizophrenics is explored in this preliminary fashion.

METHOD

The computer-based cognitive remediation program (CRP) was obtained (excluding hardware) on loan, through the co-operation of the Psychology Department of St. Michael's Hospital, Toronto, Ontario (Sunday, 1985). The program was modified, by adding tasks which were more cognitively challenging and by deleting those which required two persons to interact on the computer.

The CRP consists of a wide array of game-like programs which provides retraining of three major components of cognitive functions (i.e., visual-spatial, auditory-verbal, and general reasoning and problem-solving ability). The CRP is computer-based and the program is menu-driven. All the patient is required to do is "sign on" by providing an I.D. number. The program takes care of loading and running the individual games. The game programs automatically collect and store, on diskettes, cumulative data from each subject's performance across both games and trials. After a fixed number of trials within each game, the subject receives immediate feedback about his/her performance. All games run for 10 trials or 1 minute, depending on the nature of the game.

An initial session consisted of orientation to the CRP, and an opportunity to clarify any questions regarding

its usage. During a pilot study 4 subjects attended 24 1-1.5 hour training sessions over a period of 6-8 months. Subjects generally attended 1 session per week. A resource person was always available in the event of any problems or questions.

The CRP requires the following hardware: Commodore 64 computer, Model 1541 disk drive, Model 1702 Color Video Monitor and 1 Commodore compatible joystick.

Brief descriptions of the individual "game" programs, along with performance measures, are provided.

i Non-Verbal, Visual Spatial Skills

The following 7 games were selected to facilitate the development of such skills as visual reaction time, visual scanning, space-time estimation, response inhibition/delay, visual discrimination and perceptual judgement.

Quick Colors

A very basic visual reaction time task. The border of the screen changes colors, and the subject must press a key each time the color changes. The procedure is repeated with the center of the screen changing colors. The score is the average reaction time for border and center across trials.

Speed Racers

"Racers" (large solid squares) come from the left or right edge of the screen at random heights and at random intervals. The subject presses a key to stop them, upon

which they explode. An "X" in the center of the screen serves as a fixation point. Three speeds (i.e., levels of difficulty) are offered. The score is the average distance each racer (1=right, 2=left) travels before it is stopped.

Anticipation

The subject uses a fire-button (joystick) to shoot a rocket at a passing spaceship. The rocket is fixed at the bottom center of the screen, and travels up midline of the screen. Spaceships come in from left and right and at random heights. The subject is offered three speeds. The score is the percentage of spaceships hit from each side (1=right, 2=left).

Spy Catcher

In this task the subject must press a key when "spies" (large squares) appear, but not respond to "non-spies" (small squares). The score is the average reaction time needed to catch the spies as well as the percentage of non-spies mistakenly "caught".

Muffin-Eater Madness

The subject uses a joystick to move a brick wall up and down in order to guard 5 vertically arranged muffins from the vicious muffin eaters. Muffins are selected as being all on the right or left edge, eaters come off the opposite side of the screen. The subject is offered three speeds. The score is recorded as the number of muffins saved in a 1 minute session.

Window

The subject choses either letters or numbers as stimuli. A stimulus is visible only as it passes by a "window" (a narrow slit in the center of the screen). At any moment, only a part of the stimulus is visible as it travels from right to left. The subject is offered three speeds, and identifies each stimulus by typing the appropriate key. The score is the number of stimuli, as a percentage, correctly identified.

Cancellation

In this task the subject is presented with an array of 52 letters (4 rows of 13 letters. A target letter is randomly assigned and 11-13 target letters randomly placed. The subject uses the joystick to move a box around target letters. Scores are the percentage of targets hit, the number of false hits and the time taken to complete the task.

ii Auditory-Verbal Skills

The following auditory-verbal tasks were chosen to aid the development of fundamental auditory discrimination, word recognition, and verbal learning.

Listen 1

In this task the subject develops auditory attention to volume changes of a tone. The subject presses a key when the volume changes. Two difficulty levels are offered which corresponds to the size of the volume shift. The score is the number of volume shifts missed and well as the average reaction time across 10 trials.

Listen 2

Similar to Listen 1, except the frequency, rather than the volume, of the tone changes.

Word-Zip

Similar to the Window game, except that entire words flow past a window-slit. Words are up to 6 letters long, chosen randomly from a list of 25 words. Three speeds are offered. The subject responds by typing the word. The score is the number of words correctly identified.

Remember

This program uses sophisticated and humourous animation to teach the use of visual cues in memorizing lists (e.g., shopping lists, daily tasks). After learning visual cues, the subject is taught how to pair these with word lists, and is tested (using a recognition task) on a variety of lists). The score is the number of words correctly memorized.

iii General Reasoning & Problem-Solving

The following program was included to provide cognitive challenge in a reasoning and problem solving format. The task was also intended to facilitate self-monitoring skills, ability to use corrective feedback and cognitive flexibility.

Cypher

This game of logic is based on the popular game Master Mind. When the game begins, six red diamonds appear in the top left corner of the screen. Beneath these diamonds is a six-element color code. The object of the game is to figure out and duplicate this code in the fewest number of turns. The subject enters a guess by using different color keys located at the top of the keyboard. As each key is pressed, the color chosen appears on the screen, accompanied by a musical tone. After six keys have been pressed, the computer compares the subject's response with the hidden code beneath the diamonds. The subject's score is then displayed to the right of each guess. There are three symbols used in scoring each round. A plus sign (+) indicates that one of the guessed colors is correct and in the right location. A zero (0) means that one of the colors is correct but its location is wrong. An "at" sign (@) indicates that a color is not in the secret code. The subject is allowed a maximum of 12 attempts at solving the puzzle.

For purposes of data analysis the Sign Test of differences was employed in each individual case to pre- and post-remediation test scores in order to determine the probability that change, if found, was due to chance.

RESULTS 2

COGNITIVE REMEDIATION: Pilot Study

Demographic Characteristics	
Subject	#1 (J.O.)
Age	39 years
Education	8
SANS	59
SAPS	13
Subtype	Both

Neuropsychological Test Battery	Pre-Training Scores 04/86	Post-Training Scores 03/87	Direction of Change
WAIS- R			
Digit Span	7	7	
Vocabulary	8	8	
Comprehension	7	7	
Similarities	6	6	
Picture Completion	9	8	-
Picture Arrangement	8	7	-
Block Design	4	5	+
Digit Symbol	4	5	+
VIQ	84	84	
PIQ	82	82	
FSIQ	83	83	
Continuous Performance Test	27	34	+
Block Span	4	4	
Verbal Fluency			
FAS	28	31	+
Animal Naming			
Rey-Osterrieth Complex Figure			
Immediate	26	25	-
Delayed Recall	12	14	+
Rey-Auditory Verbal Learning			
Sum I-V	27	36	+
Recognition	10	11	+

Babcock Story Recall			
Immediate	1.5	3.5	+
Delayed Recall	2.5	3.0	+
Trails A	53.5	44.0	+
Trails B	283.0	196.0	+
Finger Agnosia			
Dominant	12	9	+
Non-Dominant	10	11	-
Grooved Pegboard			
Dominant			
Non-Dominant			
Finger Tapping			
Dominant	33	44	+
Non-Dominant	34	40	+
Speech Perception Test	11	12	-
Seashore Rhythm Test	8	6	+
Tactual Performance Test			
Total (Blocks/Minute)	1.03	1.46	+
Memory	4	7	+
Location	0	2	+
Category Test	108	78	+
IMPAIRMENT INDEX	1.00	0.86	[+]

[ ] Not included in data analysis due to non-independence p=.002

Comments: 39 yr. old paranoid schizophrenic, 25 year psychiatric history. Completed grade 8. Trained as animal care nurse, on long-term disability x 15 years. Clinical presentation includes social withdrawal, anhedonia. Completed cognitive remediation program over 11 month period, frequent missed appointments. Remained unenthusiastic throughout training, discouraged by his perceived lack of improvement on training measures. Sign Test of differences suggested significant overall improvement ($z=2.90$, $p<.01$, one-tailed) in neuropsychological performance. Degree of overall impairment remained within moderate to severely impaired range. Improvement most marked on tests of sustained attention, verbal learning and motor speed.

Demographic Characteristics

Subject	#6 (D.P.)
Age	34 years
Education	17
SANS	35
SAPS	14
Subtype	Negative

Neuropsychological Test Battery	Pre-Training Scores 06/86	Post-Training Scores 05/87	Direction of Change
WAIS- R			
Information	12	12	
Digit Span	10	11	+
Vocabulary	13	13	
Comprehension	10	9	-
Similarities	14	14	
Picture Completion	11	11	
Picture Arrangement	12	12	
Block Design	9	10	+
Digit Symbol	8	10	+
VIQ	109	109	
PIQ	99	105	[+]
FSIQ	104	107	[+]
Continuous Performance Test	37	43	+
Block Span	6	6	
Verbal Fluency			
FAS	38	35	-
Animal Naming	23	22	-
Rey-Osterrieth Complex Figure			
Immediate	35	35	
Delayed Recall	21	26	+
Rey-Auditory Verbal Learning			
Sum I-V	36	47	+
Recognition	11	15	+

Babcock Story Recall			
Immediate	12.0	11.5	-
Delayed Recall	11.5	10.0	-
Trails A	43.0	32.0	+
Trails B	105.0	98.0	+
Finger Agnosia			
Dominant			
Non-Dominant			
Grooved Pegboard			
Dominant	67	68	-
Non-Dominant	72	74	-
Finger Tapping			
Dominant	45	46	+
Non-Dominant	40	42	+
Speech Perception Test	1	2	-
Seashore Rhythm Test	7	6	+
Tactual Performance Test			
Total (Blocks/Minute)	1.95	1.95	
Memory	6	9	+
Location	3	7	+
Category Test	34	31	+
IMPAIRMENT INDEX	0.43	0.29	[+]

p= .07

Comments: 34 yr. old schizophrenic, 8 yr. psych. history. Obtained B.Sc.(Biochemistry; McMaster University, 1978). A mason until 1980, on long-term disability x 6 years. Clinical presentation includes avolition, anhedonia. Attended cognitive remediation program over 6 month period, terminated prematurely. Cognitive remediations tasks appeared insufficiently challenging to sustain interest. Sign test of differences in test scores did not suggest significant overall improvement ($z=1.50$, $p>.05$, one-tailed) in neuropsychological performance. Neuropsychological functioning remained within broad normal range. Improvement most marked on tests of sustained attention, verbal/nonverbal learning, and perceptual-motor speed. Performance on tests of verbal fluency and productivity showed slight decline.

Demographic Characteristics

Subject	#19 (J.A.)
Age	26 years
Education	11
SANS	21
SAPS	48
Subtype	Positive

Neuropsychological Test Battery	Pre-Training Scores 05/87	Post-Training Scores 12/87	Direction of Change
WAIS- R			
Digit Span	6	6	
Vocabulary	8	10	+
Comprehension	6	6	
Similarities	6	6	
Picture Completion	6	7	+
Picture Arrangement	6	6	
Block Design	6	8	+
Digit Symbol	6	9	+
VIQ	79	81	[+]
PIQ	78	84	[+]
FSIQ	77	80	[+]
Continuous Performance Test	44	41	-
Block Span	7	7	
Verbal Fluency			
FAS	36	31	-
Animal Naming			
Rey-Osterrieth Complex Figure			
Immediate	33.0	34.0	+
Delayed Recall	15.5	23.0	+
Rey-Auditory Verbal Learning			
Sum I-V	28	33	+
Recognition		14	

Babcock Story Recall			
Immediate	5.5	6.5	+
Delayed Recall	8.5	8.0	-
Trails A	34.0	22.0	+
Trails B	86.0	54.5	+
Finger Agnosia			
Dominant	1	2	-
Non-Dominant	1	1	
Grooved Pegboard			
Dominant		68.0	
Non-Dominant		72.0	
Finger Tapping			
Dominant	55	56	+
Non-Dominant	49	51	+
Speech Perception Test	1	1	
Seashore Rhythm Test	3	3	
Tactual Performance Test			
Total (Blocks/Minute)	2.75	3.14	+
Memory	8	9	+
Location	3	4	+
Category Test	69	43	+
IMPAIRMENT INDEX	0.29	0.14	[+]
			p=.003

Comments: 26 yr. old schizophrenic with 10 yr. psych. history. Completed gr. 11 with hx. of academic difficulty and failure. Labelled "slow learner" in elementary school. Worked as laborer but now unemployed x 4 yrs. Clinical presentation includes auditory hallucinations, delusional thinking (ideas of reference). Attended cognitive remediation program on irregular basis including unscheduled appointments and demonstrated fluctuating mental status. While not formally assessed, florid symptoms more apparent and behavior less appropriate during post-evaluation. Sign test of differences suggested significant overall improvement ($z=2.73$, $p<.01$, one-tailed). Overall performance remained within broad normal range, improvement in perceptual-motor speed, immed. attention span and general reasoning noted.

Demographic Characteristics

Subject	#30 (C.H.)
Age	30 years
Education	14
SANS	10
SAPS	4
Subtype	Neither

Neuropsychological Test Battery	Pre-Training Scores 06/87	Post-Training Scores 05/88	Direction of Change
WAIS- R			
Information	11	10	-
Digit Span	10	11	+
Arithmetic		8	
Comprehension	16	15	-
Similarities	10	13	+
Picture Completion	8	10	+
Picture Arrangement	9	11	+
Block Design	11	10	-
Object Assembly	9	11	+
Digit Symbol	9	11	+
VIQ	109	104	[-]
PIQ	94	104	[+]
FSIQ	102	103	[+]
Continuous Performance Test	41	44	+
Block Span	7	5	-
Verbal Fluency			
FAS	55	50	-
Animal Naming		17	
Rey-Osterrieth Complex Figure			
Immediate	34.0	36.0	+
Delayed Recall	22.0	22.5	
Rey-Auditory Verbal Learning			
Sum I-V	34	36	+
Recognition	11	15	+

Babcock Story Recall			
Immediate	9.5	10.5	+
Delayed Recall	12.5	14.0	+
Trails A	24.5	25.0	
Trails B	45.0	54.0	-
Finger Agnosia			
Dominant	2	0	+
Non-Dominant	1	0	+
Grooved Pegboard			
Dominant		62.0	
Non-Dominant		74.0	
Finger Tapping			
Dominant	50	55	+
Non-Dominant	48	55	+
Speech Perception Test	0	2	+
Seashore Rhythm Test	4	4	
Tactual Performance Test			
Total (Blocks/Minute)	1.81	3.04	+
Memory	7	7	
Location	4	4	
Category Test	24	31	-
IMPAIRMENT INDEX	0.43	0.29	[+]

p=.0485

Comments: 30 yr. old schizophrenic, presently enrolled in Business & Commerce Program at Community College (Yr.2). Had good summer employment record until 1982 but reports he "cannot tolerate" work for periods longer than 2-3 hrs due to decreased memory/concentration and motor slowing. Psychiatric symptoms, which include marked sleep disturbance and the fixed delusion of being a cartoon character, were largely in remission during the period in which the study was undertaken. He attended training sessions dutifully. Sign test of differences suggested significant overall improvement ($z=1.66$, $p<.05$, one-tailed).

DISCUSSION

Given that neuropsychological deficits, when identified, likely contribute to impaired social and occupational functioning, improvement in neuropsychological status may translate into improvement in these areas of everyday living. The present study was undertaken, initially, as an attempt to apply cognitive remediation procedures, presently used in the rehabilitation of brain damaged persons (e.g., closed head injury), to selected psychiatric patients who also show evidence of impaired brain function.

Recent data (Seidman, 1983) suggest significant structural abnormalities with associated neuropsychological deficits in at least 20-35 percent of schizophrenic patients. It has also been demonstrated that among schizophrenics with structural brain disease, CT scan abnormalities are positively correlated with degree of overall adaptive impairment as well as impaired work and occupational functioning. If significant cognitive gains could be demonstrated following a program of cognitive remediation, then it could be argued that such an approach will assist some schizophrenics in their goal of independent functioning in the community. The approach is

based on the premise that schizophrenia is amenable to the same interventions as other brain disorders.

One current conceptualization (Crow, 1980) is that there may be two distinct "syndromes" of schizophrenia. One syndrome appears to be associated with structural brain changes and predominant negative symptoms, and the other with biochemical changes and predominant positive symptoms. The two-syndrome theory also suggests that the former group is more likely to manifest neuropsychological impairment whereas the latter is described as cognitively intact. Thus it was reasonable to postulate that negative-symptom schizophrenics might be the logical target of such a rehabilitative effort.

The results of Study 1, however, did not support the position that negative-symptom schizophrenics are uniquely associated with neuropsychological impairment. In fact, level of performance comparisons between positive- and negative-symptom schizophrenics suggested mild to moderate neuropsychological impairment in each subtype. Moreover, neuropsychological impairment, when found, was generally unrelated to symptomatology. Thus the positive versus negative symptom distinction did not prove useful in predicting the presence or absence of neuropsychological impairment in this population. The need for independent, individual evaluation of neuropsychological status is therefore strongly indicated in order to understand each

patient's particular cognitive limitation and deficits. The need for individual neuropsychological evaluation in schizophrenia is also supported by the extreme heterogeneity which characterizes schizophrenic populations (Newlin, 1983). It also further validates the need for broad-based assessment of neuropsychological functioning.

With respect to cognitive remediation, the findings of this investigation stress the need for independent, individual assessment in order to delineate specific areas of neuropsychological dysfunction as well as to provide information regarding degree of overall impairment of general adaptive and problem solving ability. The neuropsychological profile can therefore be used as the basis for individual programming and for understanding who is likely to benefit from the training procedures. The profile also serves as a baseline against which changes in neuropsychological status can be compared.

The results of a preliminary effort at improving neuropsychological status in a small sample of schizophrenics produced mixed results. Three of four subjects showed evidence of improvement in neuropsychological functioning based on pre- and post-training comparisons. The data do not allow for evaluation of the relative impact of practice effects or of changes in medication status. Nevertheless, the data appeared promising inasmuch as significant improvement in

neuropsychological status may translate into improvement in various aspects of everyday functioning.

The cognitive remediation programme was generally well received by the subjects who participated in the investigation. According to information obtained in a debriefing interview, most preferred the isolated, sedentary activities at the computer to individual or group therapy settings to which they are more accustomed. On the other hand, the individual game-like programs were judged by most as either lacking sufficient challenge to sustain interest over repeated trials (e.g., Remember) or too difficult to master (e.g., Cypher). Thus, ability to adjust task complexity to skill mastery in order to provide appropriate and ongoing challenge, appears to be an desirable feature.

The computer based cognitive remediation program provided general training in visual-spatial, visual-pursuit, and auditory-verbal skills as well as general reasoning and problem solving ability. More specifically, the individual game-like programs appear to focus on the development of both selective and sustained attention, choice reaction time, perceptual-motor speed and, to a lesser extent, learning, memory and general problem solving. One limitation to the program was that it was "generic" in nature and not developed to address the limitations and deficits of any one individual. Therefore

all individuals completed all tasks whether or not the skills areas they were designed to enhance were deficient. This may have contributed to the impression that many tasks were not sufficiently challenging.

Improvement, when found, was frequently observed on neuropsychological measures which are purportedly sensitive to abilities which were highly represented in the remediation program. This runs contrary to the argument that all gains were related to practice effects and provide at least some support for the efficacy of the procedures. Improved performance, when found, tended to be most marked on tests that tap attention and perceptual-motor speed. Whether these gains generalize to extra-test situations remains open to investigation.

CONCLUSIONS

In conclusion, the results of Study 1 suggest that the positive versus negative symptom distinction is not intrinsically useful in distinguishing neuropsychologically impaired from neuropsychologically intact schizophrenics. Differences among subtypes, when found, may be more qualitative than quantitative. Furthermore, the heterogeneity of deficits among schizophrenic patients and their apparent dissociation from the patient's psychiatric presentation, underscores the need for a broad-based individual assessment of neuropsychological functioning.

Given that neuropsychological status is intimately related to social and occupational functioning, improvement in functioning may translate into improved quality of life for some schizophrenics. The results of Study 2 suggest that cognitive remediation techniques, found useful in rehabilitating some types of brain damaged patients, may also be useful to schizophrenics whose deficits also reflect underlying brain dysfunction. Whether these patients respond to cognitive remediation in a way similar to other brain-damaged patients, or to what extent improvement in neuropsychological status generalizes to situations of everyday living, are questions which remain to be answered.

APPENDIX A
SUBJECT CONSENT FORM

I, (Name of Participant), agree to take part in this study, the purpose of which has been explained to me by Dr. Meir Steiner/Dr. Alan Finlayson or Mr. Dan Bird.

I understand that I will be asked to perform a variety of tasks, such as the placement of blocks onto a formboard, that will involve concentration and memory, manipulation of materials, and some pencil and paper work. [I also agree to attend twenty-four, 1-hour sessions spread over a period of 6-8 months which involves working on a microcomputer.]

I am aware that my participation is purely voluntary and that there are no immediate benefits from being a participant in this investigation. I further understand that the total amount of time needed to collect the necessary data will involve approximately 30 hours of my time.

I also understand that I may withdraw from this study at any time, even after signing this form, and that this decision will in no way affect the care I will receive. Any information that is collected about me during this study will be kept confidential at all times. If the results are used for scientific or educational purposes, I will not be identified in any way.

---------- ----------
Signature of Participant Date

Signature of Witness

For any questions please contact:

Mr. Dan Bird, Department of Psychology
St. Joseph's Hospital, 522-4941, ext. 3697.

or Dr. Meir Steiner, Department of Psychiatry,
St. Joseph's Hospital, 522-4941, ext. 3605.

or Dr. Alan Finlayson, Department of Psychology,
Chedoke-McMaster Hospitals, 521-2100,
ext. 7537.

APPENDIX B
NEUROPSYCHOLOGICAL TEST BATTERY

MOTOR

+ Finger Tapping

SOMATO-SENSORY

Finger Agnosia

NON-VERBAL/VISUAL-SPATIAL

* Block Design
* Picture Completion
* Picture Arrangement
Rey Osterrieth Complex Figure (Copy)

VERBAL/AUDITORY

+ Speech Perception Test
Controlled Word Association
* Vocabulary
* Similarities
* Comprehension

MEMORY

Rey Auditory Verbal Learning
Rey Osterrieth Complex Figure (Recall)
Babcock Story Recall
+ Tactual Performance Test (Memory)
+ Tactual Performance Test (Location)

ATTENTION/VIGILANCE

* Digits Span (Digits Forward, Digits Backward)
Block Span
+ Seashore Rhythm Test
Trailmaking Tests (Trails A/B)
Continuous Performance Test
* Digit Symbol Substitution Test

GENERAL PROBLEM SOLVING

+ Halstead Category Test
+ Tactual Performance Test (Total Time)

GLOBAL/INTELLIGENCE

Halstead Impairment Index (Halstead-Reitan) +
WAIS-R (Verbal, Performance, Full Scale IQ) *
Deterioration Index

APPENDIX C
DEMOGRAPHIC AND NEUROPSYCHOLOGICAL CHARACTERISTICS OF SCHIZOPHRENIC SUBJECTS

Subject	Age	Sex	Educ.	I.Q. Est./Act.	* [SANS	SAPS]	Halstead Imp. Index
01 J.O.	40	M	8	97 83	59	13	1.00
02 D.L.	38	M	14	110 107	27	01	.14
03 T.K.	37	M	16	125 97	35	56	.71
04 G.R.	31	M	14	109 82	10	32	.71
05 S.O.	24	M	9	99 76	26	00	.57
06 D.P.	35	M	17	124 104	35	14	.43
07 B.C.	34	M	8	92 89	76	32	.43
08 R.B.	28	F	12	101 89	17	40	.29
09 R.B.	37	M	13	107 93	55	10	.14
10 P.R.	27	M	13	107 99	12	06	.71
11 G.C.	31	M	10	102 94	35	03	.14
12 R.R.	27	M	13	107 87	25	14	.43
13 S.R.	25	M	7	86 84	43	24	.71
14 E.B.	56	M	8	98 102	43	00	.71
15 P.J.	40	F	14	113 95	04	02	.43
16 W.O.	23	M	12	102 83	42	43	.29
17 K.S.	46	M	10	103 81	47	04	.86
18 J.H.	31	M	10	97 83	32	50	.14
19 J.A.	27	M	11	99 77	21	48	.29
20 T.S.	25	F	11	95 73	06	59	1.00

[*] Note: SANS and SAPS Total Scores are the sum of all individual items on the rating scale, not the sum of subscale ratings listed in Appendix D.

APPENDIX C (con't)
DEMOGRAPHIC AND NEUROPSYCHOLOGICAL
CHARACTERISTICS OF SCHIZOPHRENIC SUBJECTS

Subject	Age	Sex	Educ.	I.Q. Est./Act.		SANS	SAPS	Halstead Imp. Index
21 G.F.	37	M	12	106	83	25	00	.75
22 D.W.	26	M	8	90	95	21	14	.57
23 R.G.	47	M	7	91	78	20	08	1.00
24 F.B.	49	M	9	96	93	19	00	.14
25 G.G.	28	M	12	102	82	39	15	.71
26 P.B.	32	M	9	94	77	17	52	.43
27 E.S	35	M	12	104	87	06	36	.43
28 G.S	36	M	9	97	94	66	21	.57
29 W.N.	46	M	12	110	94	38	00	.57
30 C.H.	30	M	14	109	102	10	04	.43
31 D.M.	32	M	12	107	72	25	28	.86
32 B.S.	27	M	9	96	75	54	45	.86
33 D.M.	34	M	18	140	124	12	04	.14
34 O.M.	48	F	10	93	80	02	14	1.00
35 N.R.	34	M	14	109	82	50	00	.86
36 T.L.	29	M	12	105	91	13	24	.14
37 R.D.	28	M	9	94	75	13	53	.71
38 B.P.	54	F	14	104	86	61	04	.71
39 T.T.	27	M	8	90	79	69	22	.57
40 J.N.	30	M	12	103	91	35	20	.71

APPENDIX D
SCHIZOPHRENIC SUBTYPES BASED ON SANS/SAPS RATINGS AND ANDREASEN'S CRITERIA

	SANS RATINGS					SAPS RATINGS				
Subject	Sub 1	Sub 2	Sub 3	Sub 4	Sub 5	Sub 6	Sub 7	Sub 8	Sub 9	Subtype
01 J.O.	2	2	2	5	5	0	4	0	0	Both
02 D.L.	2	2	1	2	2	1	0	0	0	Neither
03 T.K.	1	1	1	4	4	5	5	4	0	Both
04 G.R.	2	0	0	0	0	4	3	0	0	Positive
05 S.O.	2	0	0	3	3	0	0	0	0	Neither
06 D.P.	1	0	4	4	0	2	2	2	0	Negative
07 B.C.	5	2	4	4	1	1	4	2	3	Both
08 R.B.	2	2	2	0	1	3	1	3	3	Neither
09 R.B.	3	2	4	4	2	0	0	3	0	Negative
10 P.R.	0	0	2	2	0	0	2	0	0	Neither
11 G.C.	2	2	4	2	4	0	1	0	0	Negative
12 R.R.	2	0	1	4	0	0	3	0	2	Neither
13 S.R.	1	2	2	5	4	3	4	2	0	Both
14 E.B.	0	0	5	5	0	0	0	0	0	Negative
15 P.J.	0	0	1	0	0	0	0	0	0	Neither
16 W.O.	4	0	3	4	2	5	3	3	0	Both
17 K.S.	2	2	4	4	2	0	0	0	2	Negative
18 J.H.	0	4	2	2	4	5	5	1	2	Both
19 J.A.	1	0	1	2	2	4	5	0	2	Positive
20 T.S.	0	0	0	0	0	5	4	2	3	Positive

Subl - Affective Flattening
Sub2 - Alogia
Sub3 - Avolition/Apathy
Sub4 - Anhedonia/Asociality
Sub5 - Attention

Sub 6 - Hallucinations
7 - Delusions
8 - Bizarre Behavior
9 - Positive Formal Thought Disorder

APPENDIX D (con't)
SCHIZOPHRENIC SUBTYPES BASED ON
SANS/SAPS RATINGS AND ANDREASEN'S CRITERIA

	SANS RATINGS					SAPS RATINGS				
	Sub 1	Sub 2	Sub 3	Sub 4	Sub 5	Sub 6	Sub 7	Sub 8	Sub 9	Subtype
21 G.F.	0	2	1	4	2	0	0	0	0	Neither
22 D.W.	2	0	3	1	2	0	4	0	2	Positive
23 R.G.	0	0	0	4	4	0	3	0	0	Negative
24 F.B.	0	0	3	3	0	0	0	0	0	Neither
25 G.G.	4	2	0	4	0	0	3	0	0	Negative
26 P.B.	0	0	0	2	2	4	4	0	4	Positive
27 E.S	0	0	2	0	0	4	4	0	0	Positive
28 G.S	4	3	4	4	2	5	2	0	0	Both
29 W.N.	2	0	4	4	2	0	0	0	0	Negative
30 C.H.	0	0	0	0	2	2	0	0	0	Neither
31 D.M.	0	0	0	3	2	0	4	0	4	Positive
32 B.S.	2	0	4	4	4	3	5	0	4	Both
33 D.M.	2	0	2	1	0	0	0	0	2	Neither
34 O.M.	0	0	0	0	2	0	0	0	4	Positive
35 N.R.	4	2	4	2	0	0	0	0	0	Negative
36 T.L.	0	0	1	2	0	3	4	0	0	Positive
37 R.D.	0	0	2	0	0	4	4	0	4	Positive
38 B.P.	4	4	3	4	2	0	0	2	0	Negative
39 T.T.	4	3	4	4	0	4	3	0	0	Both
40 J.N.	2	0	4	4	2	0	1	2	4	Both

Subl - Affective Flattening
Sub2 - Alogia
Sub3 - Avolition/Apathy
Sub4 - Anhedonia/Asociality
Sub5 - Attention

Sub 6 - Hallucinations
7 - Delusions
8 - Bizarre Behavior
9 - Positive Formal Thought Disorder

BIBLIOGRAPHY

Abrams, R. & Taylor, M.A. (1979). Differential EEG patterns in affective disorders and schizophrenia. ARCHIVES OF GENERAL PSYCHIATRY, 35, 1355-1358.

Acker, M.B. (1986). Relationships between test scores and everyday life functioning. In B.P. Uzzell & Y. Gross (Eds.) CLINICAL NEUROPSYCHOLOGY OF INTERVENTION (pp. 85-117). Boston: Martinus Nijhoff Publishing.

Alfano, D.P. & Finlayson, M.A.J. (1987). Clinical neuropsychology in rehabilitation. THE CLINICAL NEUROPSYCHOLOGIST, 1 (2) , 105-123.

American Psychiatric Association, (1980). DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, (3rd ed.). Washington, D.C., Author.

Andreasen, N.C. (1982). Negative symptoms in schizophrenia: Definition and Reliability. ARCHIVES OF GENERAL PSYCHIATRY, 1982, 39, 784-788.

Andreasen, N.C. (1983). The scale for the assessment of negative symptoms (SANS). Iowa City, Iowa: The University Of Iowa.

Andreasen, N.C. (1984a). The scale for the assessment of positive symptoms (SAPS). Iowa City, Iowa: The University of Iowa.

Andreasen, N.C. (1984b). THE BROKEN BRAIN. Toronto: Fitzhenry & Whiteside Ltd.

Andreasen, N.C. (1985a). Positive versus negative schizophrenia: A critical evaluation. SCHIZOPHRENIA BULLETIN, 11 (3), 380-389.

Andreasen, N.C. (1985b, June) Searching for brain abnormalities in schizophrenia - A review of new technologies. 2nd Annual Catherine Garwood-Jones Lecture in Schizophrenia, McMaster University, Hamilton, Ontario.

Andreasen, N., Nasrallah, H.A., Dunn, V., Olson, S.C., Grove, W.M., Ehrardt, J.C., Coffman, J.A. & Crossett,

J.H.W. (1986). Structural abnormalities in the frontal system in schizophrenia: A magnetic resonance imaging study. ARCHIVES OF GENERAL PSYCHIATRY, 43, 136-144.

Andreasen, N.C. & Olsen, S. (1982). Negative versus positive schizophrenia: Definition and validation. ARCHIVES OF GENERAL PSYCHIATRY, 39, 789-794.

Andreasen, N.C., Smith, M.R. Jacoby, C.G., Dennert, J.W. & Olsen, S.A. (1982). Ventricular enlargement in schizophrenia: Definition and prevalence. AMERICAN JOURNAL OF PSYCHIATRY, 139 (3), 292-302.

Angrist, B., Rotrosen, J. & Gershon, S. (1980). Differential effects of neuroleptics on positive versus negative schizophrenia. PSYCHOPHARMACOLOGY, 72, 17-19.

Anthony, W.A. & Farkas, M. (1982). A client outcome planning model for assessing psychiatric rehabilitation. SCHIZOPHRENIA BULLETIN, 8 (1), 13-38.

Averback, P. (1981). Structural lesions of the brain in young schizophrenics. CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES, 8 (1), 73-76.

Anthony, W.A. & Farkas, M. (1982). A client outcome model for assessing psychiatric rehabilitation interventions. SCHIZOPHRENIA BULLETIN, 8 (1), 13-38.

Babcock, H. (1930). An experiment in the measurement of mental deterioration. ARCHIVES OF PSYCHOLOGY, 117, 105.

Bach-y-Rita, P. (1980). RECOVERY OF FUNCTION: THEORETICAL CONSIDERATIONS FOR BRAIN INJURY REHABILITATION. Baltimore: University Park Press.

Bankier, R.G. (1985). Third ventricle size and dementia in schizophrenia. BRITISH JOURNAL OF PSYCHIATRY, 147, 241-245.

Barona, A., Reynolds, C.R., & Chastain, R. (1984). A demographically based index of premorbid intelligence for the WAIS-R. JOURNAL OF CLINICAL AND CONSULTING PSYCHOLOGY, 52 (5), 885-887.

Benton, A.L. (1968). Differential effects of frontal lobe disease. NEUROPSYCHOLOGIA, 6, 53-60.

Benton, A.L. & Hamsher, K. deS. (1976). MULTILINGUAL APHASIA EXAMINATION. Iowa City: University of Iowa (Mannual, revised 1978).

Bey-Yishay, Y. (1983). Cognitive remediation viewed from the perspective of a systematic clinical research program in rehabilitation. COGNITIVE REHABILITATION, 1, 4-6.

Berrios, G.E. (1985). Positive and negative symptoms and Jackson: A conceptual history. ARCHIVES OF GENERAL PSYCHIATRY, 42, 95-97.

Besson, J.A.O., Corrigan, F.M., Cherryman, G.R., & Smith, F.W. (1987). Nuclear magnetic resonance brain imaging in chronic schizophrenia. BRITISH JOURNAL OF PSYCHIATRY, 150, 161-163.

Bigelow, L.B., Donnelly, E.P., Torrey, E.F. & Lee, C.A. (1979). Assessment of clinical status of schizophrenic patients by the WAIS comprehension subtest. JOURNAL OF CLINICAL PSYCHIATRY, 40, 258-261.

Bilder, R.M., Mukherjee, S., Rieder, R.O. & Pandurangi, A.K. (1985). Symptomatic and neuropsychological components of defect states. SCHIZOPHRENIA BULLETIN, 11 (3), 409-419.

Blumer, D. (1975). Temporal lobe epilepsy and it's psychiatric significance. In D.F. Benson & D. Blumer (Eds.), PSYCHIATRIC ASPECTS OF NEUROLOGIC DISEASE (pp. 171-198). New York: Grune and Stratton.

Boucher, M.L., Dewan, M.J., Donnelly, M.P., Pandurangi, A.K., Bartell, K., Diamond, T. & Major, L.F. (1986). Relative utility of three indicies of neuropsychological impairment in a young, chronic schizophrenic population. JOURNAL OF NERVOUS AND MENTAL DISEASE, 174 (1), 44-46.

Bracy, O.L. (1986). Cognitive rehabilitation: A process Approach. COGNITIVE REHABILITATION, 4 (2), 10-17.

Braff, D.L., Glick, I.D., Johnson, M.H. & Zisook, S. (1988). The clinical significance of thought disorder across time in psychiatric patients. THE JOURNAL OF NERVOUS AND MENTAL DISEASE, 176 (4), 213-220.

Breier, A., Wolkowitz, O.M., Doran, A.R., Roy, A., Boronow, J., Hommer, D.W. & Pickar, D. (1987). Neuroleptic responsivity of negative and positive symptoms in

schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 144, 1549-1555.

Buchsbaum, M.S. (1979). Neurophysiological aspects of the schizophrenic syndrome. In L. Bellak (Ed.) DISORDERS OF THE SCHIZOPHRENIC SYNDROME (pp. 152-180). New York: Grune and Stratton.

Buchsbaum, M.S., DeLisi, L.E., Holcomb, H.H., Cappelletti, J., King, A.C., Johnson, J., Hazlett, E., Dowling-Zimmerman, S., Post, R.M., Morihisa, J., Carpenter, W., Cohen, R., Pickar, D., Weinberger, D.R., Margolin, R., & Kessler, R.M. (1984). Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorder. ARCHIVES OF GENERAL PSYCHIATRY, 41, 1159-1166.

Buchsbaum, M.S., Ingvar, D.H., Kessler, R., Waters, R.N., Cappelletti, J., King, A.C., Johnson, J.L., Manning, R.G., Flynn, R.N., Mann, L.S., Bunny, W.E., & Sokoloff, L. (1982). Cerebral glucography with positron tomography. ARCHIVES OF GENERAL PSYCHIATRY, 39, 251-259.

Buchsbaum, M.S., Kessler, R., Bunney, W.E., Cappelletti, J., Coppola, R., van Kammen, D.P., Rigal, F., Waters, R., Sokoloff, L. & Ingvar, D. (1981). Simultaneous electroencephalography and cerebral glucography with positron emission tomography in normals and patients with schizophrenia. JOURNAL OF CEREBRAL BLOOD FLOW METABOLISM, 1 (1), 457-458.

Caplan, B. (1982). Neuropsychology in rehabilitation: It's role in evaluation and intervention. ARCHIVES OF PHYSICAL AND REHABILITATIVE MEDICINE, 63, 362-366.

Carpenter, W.T., Heinrichs, D.W. & Wagman, A.M.I. (1988). Deficit and nondeficit forms of schizoprenia: The concept. AMERICAN JOURNAL OF PSYCHIATRY, 145 (5), 578-583.

Carr, E.G. & Wedding, D. (1984). Neuropsychological assessment of cerebral ventricular size in chronic schizophrenia. INTERNATIONAL JOURNAL OF CLINICAL NEUROPSYCHOLOGY, 6, 106-111.

Chelune, G.J., Heaton, R.K., Lehman, R.A.W., & Robinson, A. (1979). Level versus pattern of neuropsychological performance among schizophrenic and diffusely brain-damaged patients. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 47 (1), 155-163.

Cicerone, K.D. & Tupper, D.E. (1986). Cognitive assessment in the neuropsychological rehabilitation of head-injured adults. In B.P. Uzzell & Y. Gross (Eds.), CLINICAL NEUROPSYCHOLOGY OF INTERVENTION, (pp. 59-83). Boston: Martinus Nijhoff Publishing.

Cleghorn, J.M. (1988). A neurodiagnostic approach to schizophrenia. CANADIAN JOURNAL OF PSYCHIATRY, 33, 555-561.

Cohen, R.M., Semple, W.E. & Gross, M. (1986). Positron emission tomography. PSYCHIATRIC CLINICS OF NORTH AMERICA, 9 (1), 63-79.

Crookes, T.G. (1984). A cognitive peculiarity specific to schizophrenia. JOURNAL OF CLINICAL PSYCHOLOGY, 40 (4), 893-896.

Crow, T.J. (1980). Molecular pathology of schizophrenia: more than one disease process? BRITISH MEDICAL JOURNAL, 280, 66-68.

Crow, T.J., Cross, A.J., Johnstone, E.C. & Owen, F. (1982). Two syndromes in schizophrenia and their pathogenesis. In F.A. Henn & H.A. Nassrallah (Eds.), SCHIZOPHRENIA AS A BRAIN DISEASE (pp. 196-234). New York: Oxford University Press.

Crow, T.J., Ferrier, I.N., & Johnstone, E.C. (1986). The two-syndrome concept and neuroendocrinology of schizophrenia. PSYCHIATRIC CLINICS OF NORTH AMERICA, 9 (1), 99-113.

Damasio, A. (1979). The frontal lobes. In K. Heilman & E. Valenstein (Eds.), CLINICAL NEUROPSYCHOLOGY (pp. 360-412). New York: Oxford University Press.

Dennert, J.W. & Andreasen, N.C. (1983). CT scanning and schizophrenia: A review. PSYCHIATRIC DEVELOPMENTS, 1, 105-121.

DeMyer, K., Gilmor, R.L., Hendrie, H.C., DeMyer, W.E., Augustyn, G.T. & Jackson, R.K. (1988). Magnetic resonance brain images in schizophrenic and normal subjects: Influence of diagnosis and education. SCHIZOPHRENIA BULLETIN, 14 (1), 21-32.

Dewan, M.J., Pandurangi, A.K., Lee, S.H., Ramachandran, T., Levy, B., Boucher, M., Yozawitz, A. & Major, L. (1986). A comprehensive study of chronic schizophrenic patients I. Quantitative computed

tomography: Cerebral density, ventricle and sulcal measures. ACTA PSYCHIATRICA SCANDINAVICA, 73, 152-160.

Diamant, J.J. (1979). Neuropsychological therapy with psychiatric patients with brain damage. Paper presented at the 68th Annual Convention of the APA, Toronto, Canada (August 13).

Diller, L. (1976). A model for cognitive retraining in rehabilitation. THE CLINICAL PSYCHOLOGIST, 29, 13-15.

Diller, L. & Gordon, W.A. (1981). Interventions for cognitive deficits in brain injured adults. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 49 (6), 822-834.

Donnelly, E.F., Weinberger, D.R., Waldman, I.N. & Wyatt, R.J. (1980). Cognitive impairment associated with morphological brain abnormalities on computed tomography in chronic schizophrenic patients. THE JOURNAL OF NERVOUS AND MENTAL DISEASE, 168 (5), 305-308.

Dorval, M. & Pepin, M. (1986). Effect of playing a video game on a measure of spatial visualization. PERCEPTUAL AND MOTOR SKILLS, 62, 159-162.

Endicott, J. & Spitzer, R.L. (1978). A diagnostic interview: The schedule for affective disorders and schizophrenia. ARCHIVES OF GENERAL PSYCHIATRY, 35, 837-844.

Erlenmeyer-Kimling, L., Cornblatt, B., Friedman, D., Marcuse, Y., Rutschmann, J., Simmens, S., & Devi, S. (1982). Neurological, electrophysiological and attentional deviations in children at risk for schizophrenia. In F.A. Henn & H.A. Nashrallah (Eds.), SCHIZOPHRENIA AS A BRAIN DISEASE (pp. 61-98). Oxford University Press.

Erikson, R.C., & Binder, L.M. (1986). Cognitive deficits among functionally psychotic patients: A rehabilitation perspective. JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY, 8 (3), 257-274.

Farkas, T., Reivich, M., Alavi, A., Greenberg, J.H., Fowler, J.S., MacGregor, R.R., Christman, D.R. & Wolf, A.P. (1980). The application of 18F-deoxy-2-fluoro-D-glucose and positron emission tomography in the study of psychiatric conditions. In

J.V. Passonneau, R.A. Hawkins, W.D. Lust & F.A. Welsh (Eds.), CEREBRAL METABOLISM AND NEURAL FUNCTION (pp. 403-408). Baltimore: Williams and Wilkins.

Farmer, A., Jackson, R., McGuffin, P. & Storey, P. (1987). Cerebral ventricular enlargement in chronic schizophrenia: Consistencies and contradictions. BRITISH JOURNAL OF PSYCHIATRY, 150, 324-300.

Feuchtwanger, E. & Mayer-Gross, W. (1938). Brain injury and schizophrenia. SCHWEIZ. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 14, 17.

Finger, S. (Ed.) (1978). RECOVERY FROM BRAIN DAMAGE: RESEARCH AND MEMORY. New York, Plenum.

Finger, S., Levere, T.E., Almli, C.R. & Stein, D.G. (Eds.) (1988). BRAIN INJURY AND RECOVERY: THEORETICAL AND CONTROVERSIAL ISSUES. New York, Plenum Press.

Finlayson, M.A.J. (1977). Test complexity and brain damage at different educational levels. JOURNAL OF CLINICAL PSYCHOLOGY, 33 (1), 221-223.

Finlayson, M.A.J. (1985). Clinical neuropsychology in rehabilitation. THE ONTARIO PSYCHOLOGIST, 17 (2), 15-19.

Finlayson, M.A.J., Alfano, D.P., & Sullivan, J.F. (1987). A neuropsychological approach to cognitive remediation: Microcomputer applications. CANADIAN PSYCHOLOGY, 28 (2), 180-190.

Flor-Henry, P. (1969). Psychosis and temporal lobe epilepsy: A controlled investigation. EPILEPSIA, 10, 363-395.

Flor-Henry, P. & Yuedall, L.T. (1979). Neuropsychological investigation of schizophrenia and manic-depressive psychoses. In J. Gruselier & P. Flor-Henry (Eds.), HEMISPHERE ASYMMETRIES OF FUNCTION IN PSYCHOPATHOLOGY (pp. 341-362). Elsevier: North-Holland Biomedical Press.

Franzen, G. & Ingvar, D.H. (1975). Abnormal distribution of cerebral activity in chronic schizophrenia. JOURNAL OF PSYCHIATRIC RESEARCH, 12, 199-214.

Fredericks, R.S. & Finkel, P. (1978). Schizophrenic performance on the Halstead-Reitan battery. JOURNAL OF CLINICAL PSYCHOLOGY, 34 (1), 26-30.

Friedman, D., Erlenmeyer-Kimling, L., & Vangham, H.G. Jr. (1980). The late positive complex to unpredictable auditory events in children at high risk for schizophrenia. PSYCHOPHYSIOLOGY, 17, 310-311.

Friedman, D., Vangham, H.G. Jr., & Erlenmeyer-Kimling, L. (1979). Event-related potential investigations in children at high-risk for schizophrenia. In D. Lehmann & E. Callaway (Eds.), EVENT-RELATED POTENTIALS IN MAN: APPLICATIONS AND PROBLEMS. New York: Plenum Press.

Frith, C.D. & Done, D.J. (1988). Towards a neuropsychology of schizophrenia. BRITISH JOURNAL OF PSYCHIATRY, 153, 437-443.

Fromm-Auch, D. & Yeudall, L.T. (1983). Normative data for the Halstead-Reitan neuropsychological tests. JOURNAL OF CLINICAL NEUROPSYCHOLOGY, 5 (3), 221-238.

George, L. & Neufeld, R.W.J. (1985). Cognition and symptomatology in schizophrenia. SCHIZOPHRENIA BULLETIN, 11 (2), 264-285.

Glass, G.V. & Stanley, J.C. (1970). STATISTICAL METHODS IN EDUCATION AND PSYCHOLOGY. Englewood Cliffs, New Jersey: Prentice-Hall, Inc.

Glisky, E.L., Schacter, D.L. & Tulving, E. (1986). Learning and retention of computer-related vocabulary in memory impaired patients: Method of vanishing cues. JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY, 8 (3), 292-312.

Goetz, K.L. & van Kammen, D.P. Computerized axial tomography scans and subtypes of schizophrenia: A review of the literature (1986). THE JOURNAL OF NERVOUS AND MENTAL DISEASE, 174 (1), 31-41.

Golden, C.J., Graber, B., Coffman, J., Berg, R.A., Newlin, D.B., & Bloch, S. (1981). Structural brain deficits in schizophrenia: Identification by computed tomographic scan density measurements. ARCHIVES OF GENERAL PSYCHIATRY, 38, 1014-1017.

Golden, C.J., Hammeke, T.A. & Purisch, A.D. (1978). Diagnostic validity of a standard neuropsychological battery derived from Luria's neuropsychological tests. JOURNAL OF CLINICAL AND CONSULTING PSYCHOLOGY, 46, 1258-1265.

Golden, C.J., MacInnes, W.D., Ariel, R.N., Reudrich, S.L., Chu, C.C., Coffman, J.A., Graber, B., & Bloch, S. (1982). Cross-validation of the ability of the Luria-Nebraska Neuropsychological Test Battery to differentiate chronic schizophrenics with and without ventricular enlargement. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 50, 87-95.

Golden, C.J., Moses, J.A., Zelazowski, R., Graber, B., Zatz, L.M., Horvath, T.B., & Berger, P.A. (1980), Cerebral ventricular size and neuropsychological impairment in young chronic schizophrenics. ARCHIVES OF GENERAL PSYCHIATRY, 37, 619-623.

Goldstein, G. (1978). Cognitive and perceptual differences between schizophrenics and organics. SCHIZOPHRENIA BULLETIN, 4, 160-185.

Goldstein, G. (1986). The neuropsychology of schizophrenia. In I. Grant & K.M. Adams (Eds.), NEUROPSYCHOLOGICAL ASSESSMENT OF NEUROPSYCHIATRIC DISORDERS (pp. 147-171). Oxford University Press.

Goldstein, G. (1987). Neuropsychiatry: Interfaces between neuropsychology and psychopathology. THE CLINICAL NEUROPSYCHOLOGIST, 1 (4), 365-380.

Goldstein, G. & Halperin, K.M. (1977). Neuropsychological differences among subtypes of schizophrenia. JOURNAL OF ABNORMAL PSYCHOLOGY, 86 (1), 34-40.

Gray, J.M. & Robertson, I.H. (1988, July). Micro-computer-based attentional retraining after brain-injury: A randomized group controlled trial. Paper presented at the 11th European Conference of the International Neuropsychological Society, Lahti, Finland.

Green, M. & Walker, E. (1985). Neuropsychological performance and positive and negative symptoms in schizophrenia. JOURNAL OF ABNORMAL PSYCHOLOGY, 94 (4), 460-469.

Green, M. & Walker, E. (1986a). Attentional performance in positive- and negative-symptom schizophrenia. JOURNAL OF NERVOUS AND MENTAL DISEASE, 174 (4), 208-213.

Green, M. & Walker, E. (1986b). Symptom correlates of vulnerability to backward masking in schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 142 (2), 181-186.

Gross, Y. & Schutz, L.E. (1986). Intervention models in neuropsychology. In B.P. Uzzell & Y. Gross (Eds.), CLINICAL NEUROPSYCHOLOGY OF INTERVENTION, (pp. 179-204). Boston: Martinus Nijhoff Publishing.

Gruzelier, J., Seymour, K., Wilson, L., Jolley, A., & Hirsch, S. (1988). Impairments on neuropsychologic tests of temporohippocampal and frontohippocampal functions and word fluency in remitting schizophrenia and affective disorders. ARCHIVES OF GENERAL PSYCHIATRY, 45, 623-630.

Guenther, W. & Breitling, D. (1983). Predominant sensory motor area left hemisphere dysfunction in schizophrenia measured by brain electrical activity mapping. BIOLOGICAL PSYCHIATRY, 20 (5), 515-532.

Gur, R.E. (1979). Cognitive concomitants of hemispheric dysfunction in schizophrenia. ARCHIVES OF GENERAL PSYCHIATRY, 36, 269-274.

Gur, R.E., Resnick, S.M., Alavi, A., Gur, R.C., Caroff, S., Dann, R., Silver, F.L., Saykin, A.J., Chawluk, J.B., Kushner, M., & Reivich, M. (1987). Regional brain function in schizophrenia. I. A positron emission tomography study. ARCHIVES OF GENERAL PSYCHIATRY, 44, 119-125.

Gur, R.E. Resnick, S.M., Gur, R.C., Alvi, A., Caroff, S., Kushner, M., & Reivich, M. (1987). Regional brain function in schizophrenia. II. Repeated evaluation with positron emission tomography. ARCHIVES OF GENERAL PSYCHIATRY, 44, 126-129.

Halstead, W.C. (1947). BRAIN AND INTELLIGENCE: A QUANTITATIVE STUDY OF THE FRONTAL LOBES. Chicago: The University of Chicago Press.

Hansen, M., Paredes, J., Koczapski, A & Kogan, C. (1987). The relationship between neuroleptic dosage and cognitive functioning in chronic schizophrenic patients. CLINICAL AND INVESTIGATIVE MEDICINE, 10 (5), 368-371.

Hamilton, M. (Ed.). (1984). FISH´S SCHIZOPHRENIA, (3rd ed.). London: John Wright & Son´s.

Harris, J.G. Jr. (1975). An abbreviated form of the Phillips rating scale of premorbid adjustment in schizophrenia. JOURNAL OF ABNORMAL PSYCHOLOGY, 84 (2), 129-137.

Haug, J.O. (1962). Pneumoencephalographic studies in mental disease. ACTA PSYCHIATRICA SCANDINAVICA, 38 (Supplement 165), 1-104.

Heath, R.G. (1954). EARLY STUDIES IN SCHIZOPHRENIA. Cambridge: Harvard University Press.

Health, R.G., Franklyn, D.E. & Shraberg, D. (1979). Gross pathology of the cerebellum in patients diagnosed and treated as functional psychiatric disorders. JOURNAL OF NERVOUS AND MENTAL DISEASE, 167, 585-592.

Heaton, R.K., Baade, L.E. & Johnson, K.L. (1978). Neuropsychological test results sssociated with psychiatric disorders in adults. PSYCHOLOGICAL BULLETIN, 85 (1), 141-162.

Heaton, R.K. & Pendleton, M.G. (1981). Use of neuropsychological tests to predict adult patient's everyday functioning. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 49 (6), 807-821.

Heinrichs, D.W. & Buchanan, R.W. (1988). Significance and meaning of neurological signs in schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 145 (1), 11-18.

Herman, J., Mirsky, A.F., Ricks, N.L., & Gallant, D. (1977). Behavioral and electrographic measures of attention in children at high-risk for schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 86, 27-33.

Hill, D. (1952). EEG in episodic psychotic and psychopathic behavior. ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY, 4, 419-442.

Holzman, P.S. (1987). Recent studies of psychophysiology in schizophenia. SCHIZOPHRENIA BULLETIN, 13 (1), 49-75.

Huber, G. (1957). PNEUMOENCEPHALOGRAPHISCHE UND PSYCHOPATHOLOGISCHE BILDER BEI ENDOGEN PSYCHOSEN. Berlin: Springer.

Huber, G., Gross, G. & Shuttler, K. (1975). A long-term follow-up study pf schizophrenia: Psychiatric course of illness and prognosis. ACTA PSYCHIATRICA SCANDINAVICA, 52, 49-57

Ingvar, D.H. (1976). Functional landscapes of the dominant hemisphere. BRAIN RESEARCH, 107, 181-197.

Itil, T.M. (1977). Qualitative and quantitative EEG findings in schizophrenia. SCHIZOPHRENIA BULLETIN, 3, 61-79.

Jernigan, T.L., Zatz, L.M., Moses, J.A., & Berger, P.A. (1982). Computed Tomography in schizophrenics and normal volunteers: I. Fluid Volume. ARCHIVES OF GENERAL PSYCHIATRY, 39, 765-770.

Johnstone, E.C., Crow, T.J., Frith, C.D., Carney, M.W.P. & Price, J.S. (1978). Mechanisms of antipsychotic effect in the treatment of acute schizophrenia. LANCET, 1, 848-851.

Johnstone, E.C., Crow, T.J., Frith, C.D., Husband, J. & Kreel, L. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. THE LANCET, 2, 924-926.

Johnstone, E.C., Owens, D.R.C., Frith, C.D., & Crow, T.J. (1986). The relative stability of positive and negative features in chronic schizophrenia. BRITISH JOURNAL OF PSYCHIATRY, 150, 60-64.

Julien, R.M. (1978). A PRIMER OF DRUG ACTION, (2nd Edition). San Francisco: W.H. Freeman and Company.

Jones-Gotman, M. & Milner, B. (1977). Design fluency: The invention of nonsense drawings after focal cortical lesions. NEUROPSYCHOLOGIA, 15, 653-673.

Kaplan, R., Cleghorn, J., Brown, G.M., Szechtman, H., Garnett, S., Nahmias, C., & Szechtman, B. (1988, January). Clinical and PET correlates of neuropsychological deficits in acutely ill and ambulatory schizophrenic men. Paper presented at the 16th Annual Meeting of the International Neuropsychological Society, New Orleans.

Kaufman, L., Crooks, L.E. & Margulis, R.R. (Eds.) (1982). NUCLEAR MAGNETIC RESONANCE IMAGING IN MEDICINE. New York: Igaku-Shoin Ltd.

Kay, S.R., Flazbein, A. & Opler, L.A. (1987). The positive and negative syndrome scale (PANSS) for Schizophrenia. SCHIZOPHRENIA BULLETIN, 13 (2), 261-276.

Kay, S.R. & Opler, L.A. (1987). Letters to the editor; Reply to Volkow et al., 1987. AMERICAN JOURNAL OF PSYCHIATRY, 144 (10), 1367.

Kay, S.R., Opler, L.A. & Fiszbein, A. (1986). Significance Of positive and negative syndromes in chronic schizophrenia. BRITISH JOURNAL OF PSYCHIATRY, 149, 439-448.

Kiev, A., Chapman, L.F., Guthrie, T.C. & Wolfe, H.G. (1962). The highest integrative functions and diffuse cerebral atrophy. NEUROLOGY, 12, 385-393.

Kinney, D.K., Woods, B.T. & Yurgelun-Todd, D. (1986). Neurologic abnormalities in schizophrenic patients and their families. ARCHIVES OF GENERAL PSYCHIATRY, 43, 665-668.

Kling, A., Lancaster, J. & Benitone, J. (1970). Amygdalectomy in the free ranging vervet (cercopithecus aethiops). JOURNAL OF PSYCHIATRIC RESEARCH, 7, 191-199.

Klonoff, H., Fibiger, C.H., & Hutton, G.H. (1970). Neuropsychological patterns in chronic schizophrenia. THE JOURNAL OF NERVOUS AND MENTAL DISEASE, 150 (4), 291-300.

Kolb, B. & Whishaw, I.Q. (1983). Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal, or parietal function in neurological patients. THE JOURNAL OF NERVOUS AND MENTAL DISEASE, 171 (7), 435-443.

Kraepelin, E. (1971). R.M. Barclay (trans.), DEMENTIA PRAECOX AND PARAPHRENIA, (8th ed.). Huntington, New York: Krieger Publishing.

Kraepelin, E. (1976). R.M. Barclay (trans.), MANIC-DEPRESSIVE INSANITY AND PARANOIA, (8th ed.). Huntington, New York: Krieger Publishing.

Kurlychek, R.T. & Glang, A.E. (1984). The use of microcomputers in the cognitive rehabilitation of brain-injured persons. In M.D. Schwartz (Ed.) USING COMPUTERS IN CLINICAL PRACTICE: PSYCHOTHERAPY AND MENTAL HEALTH APPLICATIONS. New York: The Haworth Press.

Largen, J.W., Smith, R.C., Calderon, M., Baumgartner, R., Lu, R-B., Schooler, J.C. & Ravichandran, G.K. (1984). Abnormalities of brain structure and density in schizophrenia. BIOLOGICAL PSYCHIATRY, 19 (7), 991-1013.

LaRusso, L. (1985). Sensitivity of paranoid patients to non-verbal cues. JOURNAL OF ABNORMAL PSYCHOLOGY, 87, 463-471.

Lewine, R.R.J. (1985). Negative symptoms in schizophrenia: Editor's introduction. SCHIZOPHRENIA BULLETIN, 11 (3), 361-363.

Lezak, M.D. (1983). NEUROPSYCHOLOGICAL ASSESSMENT (2nd ed.). Oxford University Press.

Liddle, P.F. (1987). The symptoms of chronic schizophrenia: A re-examination of the positive-negative dichotomy. BRITISH JOURNAL OF PSYCHIATRY, 151, 145-151.

Lohr, J.B. & Jeste, D.V. (1986). Cerebellar pathology in schizophrenia? A neurometric study. BIOLOGICAL PSYCHIATRY, 21, 865-875.

Lonnum, A. (1966). THE CLINICAL SIGNIFICANCE OF CENTRAL CEREBRAL VENTRICULAR ENLARGEMENT. Oslo, Sweden: Universitetsforlaget.

Luchins, D.J. (1982). Computed tomography in schizophrenia: Disparities in the prevalence of abnormalities. ARCHIVES OF GENERAL PSYCHIATRY, 39, 859-860.

Luchins, D.J., Weinberger, D.R. & Wyatt, R.J. (1979). Schizophrenia: Evidence of a subgroup with reversed cerebral asymmetry. ARCHIVES OF GENERAL PSYCHIATRY, 36, 1309-1311.

Lynch, W.J. (1982). The use of electronic games in cognitive rehabilitation. In L.E. Trexler (Ed.) COGNITIVE REHABILITATION: CONCEPTUALIZATION AND INTERVENTION (pp. 263-274). New York: Plenum Press.

Lynch, W.J. (1983). Cognitive retraining using microcomputer games and commercially available software. COGNITIVE REHABILITATION, 1, 19-22.

Magaro, P.A. (1978). Information processing and hemispheric specialization in schizophrenia and paranoia. Paper presented at the APA convention, Toronto, August.

Malec, J. (1978). Neuropsychological assessment of schizophrenia versus brain damage: A review. JOURNAL OF NERVOUS AND MENTAL DISEASE, 166, 507-516.

Malloy, T.E., Mitchell, C. & Gordon, O.E. (1987). Training cognitive strategies underlying intelligent problem solving. PERCEPTUAL AND MOTOR SKILLS, 64, 1039-1046.

Matarazzo, J.D., Matarazzo, R.G., Wiens, A.N., Gallo, A.E. & Klonoff, H. (1976). Retest reliability of the Halstead impairment index in a normal, a schizophrenia, and two samples of organic patients. JOURNAL OF CLINICAL PSYCHOLOGY, 32 (2), 339-349.

Mathew, R.J., Meyer, J.S., Francis, D.J., Schoolar, J.C., Weinman, M. & Mortel, K.F. (1981). Regional cerebral blood flow in schizophrenia: A preliminary report. AMERICAN JOURNAL OF PSYCHIATRY, 138, 112-113.

Matthews, C.G. & Brooker, H.E. (1972). Pneumoencephalographic measurements and neuropsychological test performance in human adults. CORTEX, 8, 69-92.

McGlashan, T.H. (1984). Testing four diagnostic systems for schizophrenia. ARCHIVES OF GENERAL PSYCHIATRY, 41, 141-144.

McKenna, P.J. (1987). Pathology, phenomenology and the dopamine hypothesis of schizophrenia. BRITISH JOURNAL OF PSYCHIATRY, 151, 288-301.

Meltzer, H.Y. & Locascio, J. (1987). Positive and negative subtypes in schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 144 (10), 1366-1367.

Mettler, F.A. & Crandell, A. (1959). Relation between parkinsonism and psychiatric disorder, 129, 551.

Miller, E. (1984) RECOVERY AND MANAGEMENT OF NEUROPSYCHOLOGICAL IMPAIRMENTS. New York: John Wiley & Sons.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. BRITISH MEDICAL BULLETIN, 27, 272-277.

Mirsky, A.F. (1969). Neuropsychological basis of schizophrenia. ANNUAL REVIEW OF PSYCHOLOGY, 20, 321-348.

Moriguchi, I. (1981). A study of schizophrenic brains by computerized tomography scans. FOLIA PSYCHIATRY NEUROL. JAPAN, 35, 55-72.

Morihisia, J.M., Duffy, F.H. & Wyatt, R.J. (1983). Brain electrical activity mapping (BEAM) in schizophrenic patients. ARCHIVES OF GENERAL PSYCHIATRY, 40, 719-728.

Morihisia, J.M. & McAnulty, G.B. (1985). Structure and function: Brain electrical activity mapping and computer tomography in schizophrenia. BIOLOGICAL PSYCHIATRY, 20, 3-19.

Morris, J. & Bleiberg, J. (1986). Neuropsychological rehabilitation and traditional psychotherapy. INTERNATIONAL JOURNAL OF CLINICAL NEUROPSYCHOLOGY, 8 (3), 133-135.

Morstyn, R., Duffy, F.H. & McCarley, R.W. (1983). Period altered P300 topography in schizophrenia. ARCHIVES OF GENERAL PSYCHIATRY, 40, 729-734.

Moscarelli, M., Cesana, B.M., Ciussani, S., Novati, N.C. & Cazzulo, C.L. (1989). Ventricle-brain ratio and alogia in 19 young patients with chronic negative and positive schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 146, 2, 257-258.

Murray, R. (1985). Schizophrenia. In P. Hill, R. Murray & A. Thorley (Eds.), ESSENTIALS OF POSTGRADUATE PSYCHIATRY (2nd ed.). London, England: Grune and Stratton, Inc.

Naeser, M.A., Levine, H.L., Benson, D.F., Struss, D.T. & Weir, W.S. (1981) Frontal leukotomy size and hemispheric asymmetries on computerized tomographic scans of schizophrenics with variable recovery. ARCHIVES OF NEUROLOGY, 38, 30-37.

Nashold, B.S. Jr., Slaughter, D.G. & Gills, J.P. (1969). Sensation evoked by stimulation of the midbrain in man. JOURNAL OF NEUROSURGERY, 30, 14-24.

Nasrallah, H.A., Andreasen, N.C., Coffman, J.A., Olson, S.C., Dunn, V.D., Ehrardt, J.C., & Chapman, S.M. (1986). A controlled magnetic resonance imaging study of corpus callosum thickness in schizophrenia. BIOLOGICAL PSYCHIATRY, 21, 274-282.

Nashrallah, H.A., Jacoby, C.G. & McCalley-Whitters, M. (1981). Cerebellar atrophy in schizophrenia and mania. LANCET, 1, 1102.

Newlin, D. (1983) Assessing brain damage in schizophrenia. In C.J. Golden, J.A. Moses, Jr., J.A. Coffman, R.

Miller & F.D. Striker (Eds), CLINICAL NEUROPSYCHOLOGY: INTERFACE WITH NEUROLOGIC AND PSYCHIATRIC DISORDERS (pp. 197-220). New York: Grune & Stratton.

Obiols, J.E., Marcos, T. & Salamero, M. (1987). Ventricular enlargement and neuropsychological testing in schizophrenia. ACTA PSYCHIATRICA SCANDINAVICA, 76, 199-202.

Ontario Council of Health (1980). Computerized Tomography (CT).

Osterrieth, P.A. (1944). Le test de copie d'une figure complexe. ARCHIVES DE PSYCHOLOGIE, 30, 206-356.

Pandurangi, A.K., Dewan, M.J., Boucher, M., Levy, B., Ramachandran, T., Bartell, K., Bick, P.A., Phelps, B.H. & Major, L. (1985). A comprehensive study of chronic schizophrenic patients II. Biological, neuropsychological, and clinical correlates of CT abnormality. ACTA PSYCHIATRICA SCANDINAVICA, 73, 161-171.

Parsons, O.A. & Klein, H.P. (1970). Concept identification and practice in brain-damaged and process-reactive schizophrenic groups. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 35 (3), 317-323.

Pfolh, B. & Winokur, G. (1982). Schizophrenia: Course And Outcome. In F.A. Henn & H.A. Nashrallah (Eds.), SCHIZOPHRENIA AS A BRAIN DISEASE (pp. 26-39). Oxford University Press.

Pogue-Geile, M.F. & Harrow, M. (1985). Negative symptoms in schizophrenia: Their longitudinal course and prognostic importance. SCHIZOPHRENIA BULLETIN, 11 (3), 427-438.

Ponsford, J.L. & Kinsella, G. (1988). Evaluation of a remedial programme for attention deficits following closed head injury. JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY, 10 (6), 693-708.

Pope, H. & Lipinski, J. (1978). Differential diagnosis of schizophrenia and manic-depressive illness. ARCHIVES OF GENERAL PSYCHIATRY, 35, 811-836.

Posser, E.S., Csernansky, J.G., Kaplan, J., Thiemann, S., Becker, T.J., & Hollister, L.E. (1987). Depression, parkinsonian symptoms, and negative symptoms in schizophrenics treated with neuroleptics. THE JOURNAL

OF NERVOUS AND MENTAL DISEASE, 175 (2), 100-105.

Prigatano, G.P. (1987). Neuropsychological deficits, personality variables and outcome. In M. Ylvisaker & E.M.R. Gobble (Eds.), COMMUNITY RE-ENTRY FOR HEAD INJURED ADULTS, (pp. 1-23). Boston: College-Hill Press.

Prigatano, G.P., Fordyce, D.J., Zeiner, H.K., Roueche, J.R., Pepping, M. & Wood, B.C. (1984). Neuropsychological rehabilitation after closed-head injury in young adults. JOURNAL OF NEUROLOGY, NEUROSURGERY, AND PSYCHIATRY, 47, 505-513.

Prigatano, G.P., Pepping, M. & Klonoff, P. (1986). Cognitive, personality, and psychosocial factors in the neuropsychological assessment of brain-injured patients. In B.P. Uzzell & Y. Gross (Eds.), CLINICAL NEUROPSYCHOLOGY OF INTERVENTION, (pp. 135-166). Boston: Martinus Nijhoff Publishing.

Pugh, M. & Bigler, E.D. (1986). Schizoprenia and prior history of "MBD": Neuropsychological findings. THE INTERNATIONAL JOURNAL OF CLINICAL NEUROPSYCHOLOGY, 8 (1), 22-26.

Purisch, A.D., Golden, C.J., & Hammeke, T.A. (1978). Discrimination between schizophrenic and brain-damaged patients using the Luria-Nebraska Neuropsychological Battery. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 46, 1266-1273.

Pyke, J.M. (1986). Schizophrenia: Current concepts. THE CANADIAN NURSE, 14-18.

Rappaport, M., Hall, K.M., Hopkins, K., Belleza, T. & Cope, D.N. (1982). Disability rating scale for severe head trauma: Coma to community. (1982). ARCHIVES OF PHYSICAL AND REHABILITATION MEDICINE, 63, 118-123.

Reitan, R.M. (1955). The relation of the trail making test to organic brain damage. JOURNAL OF NERVOUS AND MENTAL DISEASE, 121, 463-467.

Reitan, R.M. (1979). NEUROPSYCHOLOGY AND REHABILITATION. Author. Reitan Neuropsychological Laboratory, 1338 E. Edson Street, Tucson, AZ, 85719, U.S.A.

Reitan, R.M. (1986). THE NEUROPSYCHOLOGICAL DEFICIT SCALE. Author. Reitan Neuropsychological Laboratory, 1338 E. Edson Street, Tucson, AZ, 85719, U.S.A.

Reitan, R.M. (1988). TRAUMATIC BRAIN INJURY, VOLUME III, RECOVERY AND REHABILITATION. Tucson, Arizona: Neuropsychology Press.

Reitan, R.M. and Davison, L.A. (1974). CLINICAL NEUROPSYCHOLOGY: CURRENT STATUS AND APPLICATIONS. New York: Hemisphere Publishing Company.

Reitan, R.M. and Wolfson, D. (1985). THE HALSTEAD-REITAN NEUROPSYCHOLOGICAL TEST BATTERY: THEORY AND CLINICAL INTERPRETATION. Tucson, Arizona: Neuropsychology Press.

Reveley, M.A. (1985). Ventricular enlargement in schizophrenia: The validity of computerised tomographic findings. BRITISH JOURNAL OF PSYCHIATRY, 147, 233-240.

Rey, A. (1941). L´examen psychologique dans les cas d´encephalopathie tramatique. ARCHIVES DE PSYCHOLOGIE, 28 (112), 286-340.

Rey, A. (1964). L´EXAMEN CLINIQUE EN PSYCHOLOGIE. Paris: Presses Universitaries de France.

Rieder, R.O., Donnelly, E.F., Herdt, J.R. & Waldman, I.N. (1979). Sulcal prominence in young chronic schizophrenia patients. PSYCHIATRIC RESEARCH, 1, 1-8.

Robertson, I.H. & Gray, R.M. (1988, July). A randomized controlled trial of computer-based cognitive rehabilitation for unilateral neglect. Paper presented at the 11th European Conference of the International Neuropsychological Society, Lahti, Finland.

Roemer, R.A., Shagass, C., Straumanis, J.J. & Amadeo, M. (1978). Pattern evoked potential measurements suggesting lateralized hemispheric dysfunction in chronic schizophrenia. BIOLOGICAL PSYCHIATRY, 13, 185-202.

Rosenthal, R. & Bigelow, L.B. (1972). Quantitative brain measurements in chronic schizophrenica. BRITISH JOURNAL OF PSYCHIATRY, 121, 259-264.

Rossi, A., Stratta, P., Gallucci, M., Passarello, R. & Casacchia, M. (1988). Brain morphology in schizophrenia by magnetic resonance imaging (MRI). ACTA PSYCHIATRICA SCANDINAVICA, 77, 741-745.

Rossi, A., Stratta, P., Gallucci, M., Passarello, R. & Casacchia, M. (1989). Quantification of corpus callosum and ventricles in schizophrenia with nuclear magnetic resonance imaging: A pilot study. AMERICAN JOURNAL OF PSYCHIATRY, 146 (1), 99-101.

Rosvold, H.E., Mirsky, A.F., Sarason, I., Bransome, E.D. Jr. & Beck, L.H. (1956). A continuous performance test of brain damage. JOURNAL OF CONSULTING PSYCHOLOGY, 20 (5), 343-350.

Ryan, E.R., Bell, M.D. & Metcalf, J.C. (1982). The development of a rehabilitation psychology program for persons with schziophrenia: Changes in the treatment environment. REHABILITATION PSYCHOLOGY, 27 (2), 67-85.

Schacter, D., Rich, S. & Stampp, A. (1985). Remediation of memory disorders: Experimental evaluation of the spaced retrieval technique. JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY, 7 (1), 79-96.

Scherzer, B.P. (1986). Rehabilitation following severe head trauma: Results of a three-year program. ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION, 67, 366-374.

Schwartzman, A.E. & Douglas, V.I. (1962). Intellectual loss in schizophrenia: Part I. CANADIAN JOURNAL OF PSYCHOLOGY, 16, 1-10.

Seidman, L.J. (1983). Schizophrenia and brain dysfunction: An integration of recent neurodiagnostic findings. PSYCHOLOGICAL BULLETIN, 94 (2), 195-238.

Sena, D.A., Sunde, R.R., & Sena, H.A. (1987). Cognitive rehabilitation effects on psychobehavioral functioning of brain-injured patients and family members. Paper presented at the tenth International Neuropsychological Society, European Conference, Barcelona, Spain, July.

Shelton, R.C., Karson, C.N., Doran, A.R., Pickar, D., Bigelow, L.B. & Weinberger, D.R. (1988). Cerebral structural pathology in schizophrenia: Evidence for a selective prefrontal cortical defect. AMERICAN JOURNAL OF PSYCHIATRY, 145 (2), 154-163.

Silverstein, M.L. & Arzt, A.T. (1985). Neuropsychological dysfunction in schizophrenia: Relation to associative thought disorder. THE JOURNAL OF NERVOUS AND MENTAL

DISEASE, 173 (6), 341-346.

Silverstein, M.L. & Zerwic, M.J. (1985). Clinical psychopathologic symptoms in neuropsychologically impaired and intact schizophrenics. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 53 (2), 267-268.

Smith, A. (1964). Mental deterioration in chronic schizophrenia. JOURNAL OF NERVOUS AND MENTAL DISEASE, 139, 479-487.

Snezhnevsky, A.V. (1968). The symptomatological clinical forms and nosology of schizophrenia. In J.G. Howells (Ed.), MODERN PERSPECTIVES IN WORLD PSYCHIATRY. Edinborough: Oliver and Boyd.

Sommers, A.A. (1985). "Negative symptoms": Conceptual and methodological problems. SCHIZOPHRENIA BULLETIN, 11 (3), 364-379.

Sohlberg, M.M. & Mateer, C.A. (1987). Effectiveness of an attention training program. JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY, 9 (2), 117-130.

Sohlberg, M.M. & Mateer, C.A. (1989). INTRODUCTION TO COGNITIVE REHABILITATION: THEORY AND PRACTICE. New York: The Gilford Press.

Spiers, P.A. (1981). Have they come to praise Luria or to bury him? The Luria-Nebraska controversy. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 49, 331-341.

Spitzer, R.L., Endicott, J & Robins, E. (1978). Research diagnostic criteria: Rationale and reliability. ARCHIVES OF GENERAL PSYCHIATRY, 35, 773-782.

Stevens, J.R. (1982). Neurology and neuropathology of schizophrenia. In F.A. Henn & H.A. Nashrallah (Eds.), SCHIZOPHRENIA AS A BRAIN DISEASE (pp. 112-147). Oxford University Press.

Stevens, J.R., Mark, U.H., Ervin, F., Pacheco, P., & Suematsu, K. (1969). Deep temporal stimulation in man. ARCHIVES OF NEUROLOGY, 21, 157-169.

Suddath, R.L., Casanova, M.F., Goldberg, T.E., Daniel, D.G., Kelsoe, J.R. Jr. & Weinberger, D.R. (1989). Temporal lobe pathology in schizophrenia: A quantitative magnetic resonance imaging study. AMERICAN JOURNAL OF PSYCHIATRY, 146 (4), 464-472.

Stoudemire, A., Nelson, A. & Houpt, J.L. (1983). Interictal schizophrenia-like psychoses in temporal lobe epilepsy. PSYCHOSOMATICS, 24 (4), 331-339.

Sunday, E. (1985). Computer-based cognitive retraining system [computer programme]. St. Michael's Hospital, Toronto, Ontario, M5B 1W8.

Sunde, R.R., Sena, D.A. & Sena, H.M. (1987). Cognitive rehabilitation effects on personalities of brain-impaired patients and family members. Paper presented at the tenth International Neuropsychological Society, European Conference, Barcelona, Spain, July.

Szechtman, H., Nahmias, C., Garnett, E.S., Firnau, G., Brown, G.M., Kaplan, R.D. & Cleghorn, John M. (1988). Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. ARCHIVES OF GENERAL PSYCHIATRY, 45, 523-532.

Szekeres, S.F., Ylvisaker, M. & Cohen, S.B. (1987). A framework for cognitive rehabilitation therapy. In M. Tlvisaker & E.M.R. Gobble (Eds.), COMMUNITY RE-ENTRY FOR HEAD-INJURED ADULTS, (pp. 87-136), Boston: College-Hill Press.

Tandon, R. & Greden, J.F. (1989). Positive and negative syndromes in schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 146 (3), 407.

Tatetsu, S. (1964). A contribution to the morphological background of schizophrenia: With special reference to findings in the telencephalon. ACTA NEUROPATHOLOGICA, 3, 558-571.

Taylor, A.E., Saint-Cyr, J.A. & Lang, A.E. (1987). Parkinson's Disease: Cognitive changes in relation to treatment response. BRAIN, 110, 35-51.

Taylor, A.E., Saint-Cyr, J.A. & Lang, A.E. (1988). Idiopathic parkinson's disease: Revised concepts of cognitive and affective status. THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES, 15 (2), 106-113.

Taylor, D.C. (1977). Epileptic experience, schizophrenia and the temporal lobe. McLEAN HOSPITAL JOURNAL, 22-39.

Taylor, E.M. (1959). THE APPRAISAL OF CHILDREN WITH CEREBRAL DEFICITS. Cambridge, Massachusetts: Harvard University Press.

Taylor, M.A. & Abrams, R. (1984). Cognitive impairment in schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 141 (2), 196-201.

Taylor, M.A. & Abrams, R. (1987). Cognitive impairment patterns in schizophrenia and affective disorder. JOURNAL OF NEUROLOGY, NEUROSURGERY, AND PSYCHIATRY, 50, 895-899.

Taylor, M.A., Abrams, R., & Gaztanga, P. (1975). Manic-depressive illness and schizophrenia: A partial validation of research diagnostic criteria utilizing neuropsychological testing. COMPREHENSIVE PSYCHIATRY, 16 (1), 91-96.

Torrey, E.F. & Peterson, M.R. (1976). The viral hypothesis of schizophrenia. SCHIZOPHRENIA BULLETIN, 2, 136-146.

Trexler, L.E. (Ed.) (1983). COGNITIVE REHABILITATION: CONCEPTUALIZATION AND INTERVENTION. New York: Plenum Press.

Trexler, L.E. (1987). Neuropsychological rehabilitation in the United States. In M. Meier, A. Benton, & L. Diller (Eds.). NEUROPSYCHOLOGICAL REHABILITATION, New York: Gilford.

Tsang, M.T. (1982). Schizophrenic syndromes: The search for subgroups in schizophrenia with brain dysfunction. In F.A. Henn & H.A. Nasrallah (Eds.), SCHIZOPHRENIA AS A BRAIN DISEASE (pp. 14-25). Oxford University Press.

Uzzell, B.P. (1986). Pathophysiology and behavioral recovery. In B.P. Uzzell & Y. Gross (Eds.), CLINICAL NEUROPSYCHOLOGY OF INTERVENTION, (pp. 3-18). Boston: Martinus, Nijhoff Publishing.

Vianna, U. (1975). The EEG in schizophrenia. In M.H. Lader (Ed.), STUDIES OF SCHIZOPHRENIA (No. 10 in British Journal of Psychiatry Special Public Series). Kent, England: Headly.

Volkow, N.D., Wolf, A.P., Van Gelder, P., Brodie, J.D., Overall, J.E., Cancro, R. & Gomez-Mont, F. (1987). Positive and negative subtypes of schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 144 (10), 1367-1368.

Walker, E.F. & Harvey, P.D. (1986). Positive and negative symptoms in schizophrenia: Attentional performance correlates. PSYCHOPATHOLOGY, 19, 294-302.

Walker, E.F., Harvey, P.D. & Perlman, D (1988). The positive/negative symptom distinction in psychoses: A replication and extension of previous findings. THE JOURNAL OF NERVOUS AND MENTAL DISEASE, 176 (6), 359-363.

Watson, C.G., Thomas, R.W., Anderson, D. & Felling, J. (1968). Differentiation of organics from schizophrenics at two chronicity levels by use of the Reitan-Halstead organic test battery. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 32, 679-684.

Wechsler, D. (1981). WECHSLER ADULT INTELLIGENCE SCALE-REVISED. New York: The Psychological Corporation.

Wechsler, D. (1987). WECHSLER MEMORY SCALE-REVISED. New York: The Psychological Corporation.

Weinberger, D.R. (1984). CAT scan findings in schizophrenia: Speculation on the meaning of it all. JOURNAL OF PSYCHIATRIC RESEARCH, 18, 477-490.

Weinberger, D.R., Berman, K.F. & Zec, R.F. (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. ARCHIVES OF GENERAL PSYCHIATRY, 43, 114-124.

Weinberger, D.R., Cannon-Spoor, E., Potkin, S.G. & Wyatt, R.J. (1980). Poor premorbid adjustment and CT scan abnormalities in chronic schizophrenia. AMERICAN JOURNAL OF PSYCHIATRY, 1980, 137, 1410-1413.

Weinberger, D.R. & Wyatt, R.J. (1982). Brain morphology in schizophrenia: In vivo studies. In F.A. Henn and H.A. Nashrallah (Eds.) SCHIZOPHRENIA AS A BRAIN DISEASE (pp 148-175), Oxford University Press.

Weinberger, D.R., Torrey, E.F., Neophytides, A.N., & Wyatt, R.J. (1979a). Lateral cerebral ventricular enlargement in chronic schizophrenia. ARCHIVES OF GENERAL PSYCHIATRY, 36, 735-739.

Weinberger, D.R., Torrey, E.F., Neophytides, A.N., and Wyatt, R.J. (1979b). Structural abnormalities in the cerebral cortex of chronic schizophrenic patients. ARCHIVES OF GENERAL PSYCHIATRY, 36, 935-939.

Weinberger, D.R., Torrey, E.F. and Wyatt, R.J. (1979). Cerebellar atrophy in chonic schizophrenia. THE

LANCET, 718-719.

Weinstein, M.R. (1954). Histopathological changes in the brain in schizophrenia: A critical review. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, 71, 538-553.

Wexler, B.E. (1980). Cerebral laterality and psychiatry: A review of the literature. AMERICAN JOURNAL OF PSYCHIATRY, 137 (3), 279-291.

Widen, L., Bergstrom, M. & Blomquist, G. (1983). Positron emission tomography studies of brain energy metabolism in schizophrenia. In W.D. Heiss & M.E. Phelps (Eds.), POSITRON EMISSION TOMOGRAPHY OF THE BRAIN (pp. 192-195), New York: Springer-Verlag.

Williams, A.O., Reveley, M.A., Kolowowshi, T., Arden, M. & Mandelbrote, B.M. (1985). Schizophrenia with good and poor outcome: II. Cerebral ventricular size and it's clinical significance. BRITISH JOURNAL OF PSYCHIATRY, 16, 239-246.

Williamson, P. & Mamelak, M. (1987). Frontal spectral EEG findings in acutely ill schizophrenics. BIOLOGICAL PSYCHIATRY, 22 (8), 1021-1024.

Wilson, R.S., Rosenbaum, G. & Brown, G. (1979). The problem of premorbid intelligence in neuropsychological assessment. JOURNAL OF CLINICAL NEUROPSYCHOLOGY, 1 (1), 49-53.

Young, T. & Williamson, P. (1986). Brain imaging and functional mental disorders. CANADIAN JOURNAL OF PSYCHIATRY, 131, 675-680.

Yozawitz, A. (1986). Applied neuropsychology in a psychiatric center. In I. Grant & K.M. Adams (Eds.), NEUROPSYCHOLOGICAL ASSESSMENT OF NEUROPSYCHIATRIC DISORDERS (pp. 121-146). Oxford University Press.

Zec, R.F., & Weinberger, D.R. (1986). Relationship between CT findings and neuropsychological performance in chronic schizophrenia. PSYCHIATRIC CLINICS OF NORTH AMERICA, 9 (1), 49-61.